Tetrahedron Letters No.57, pp. 6019-6022, 1968. Pergamon Press. Printed in Great Britain.

STEREOCHEMISTRY OF GRAYANOTOXIN

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(Received in Japan 1 August 1968; received in UK for publication 25 October 1968)

Stereochemical formulae 1 and 1' have been proposed for Grayanotoxin (hereafter G) I by Kakisawa et al.1) and by Tallent2) respectively while a conflicting formula 2 has been assigned to G-II (desacetylanhydro G-I3)) by Kumazawa et al.4) It appeared to us interesting to obtain further information about the stereochemistry of the toxins, particularly of the perhydroazulene moiety, since cis perhydroazulene is predicted5) to exist in two separate conformations 3 and 4. In this paper we should like to present the results which led to the stereochemical structure 5 with the type 3 hydroazulene for G-I. G-I affords on CrO_3 oxidation didehydro G-I, to which the structure 6 has been assigned.6) However, the doublet peak (1 H) at τ 6.42 (J=12.6 Hz) in the n m r spectrum (Fig. 1) of this compound clearly indicates the presence of a $—COCH_2\text{-}C{\equiv}C_3$ system, which is consistent with 7 but not with 6. Similarly G-II gives a tridehydro compound $C_{20}H_{26}O_5$ 8 (m.p. 224-225°, n m r Fig. 2) on CrO_3-pyridine oxidation. The singlet peak at τ 3.93 in the spectrum of didehydro G-I is doubtless attributable to the C-14 proton, and the small coupling constant ($J \simeq 0$) indicates that the C-14 proton is axial. The remarkably low τ value 3.93 suggests either the C-10 hydroxyl group or C-6 carbonyl group or both are close to the C-14 proton. Examination of B-C-D ring models of possible conformations however shows that the C-6 carbonyl group connot be at a position which causes a low field shift. Therefore, the C-10 hydroxyl group and C-14 proton must be situated at a close position. Only the conformation with B/C cis and C-9H/C-10 OH trans configuration satisfies this condition.

Fig. 1 60MHz $CDCl_3$

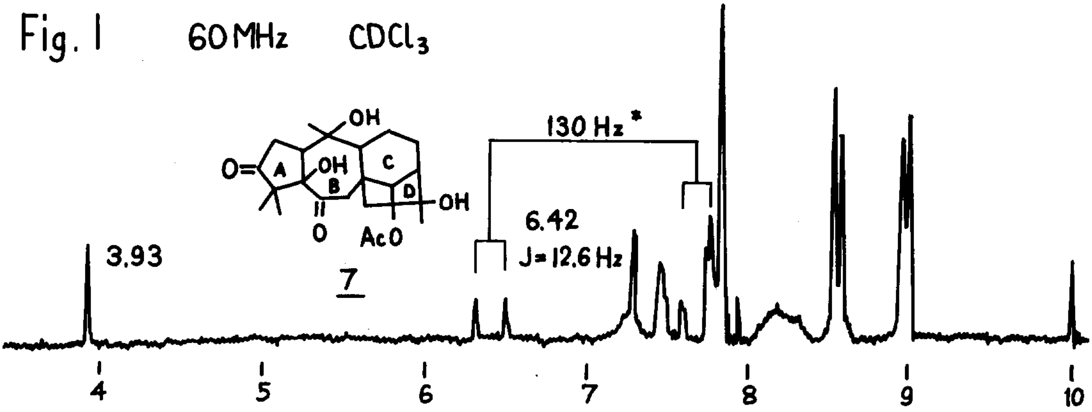
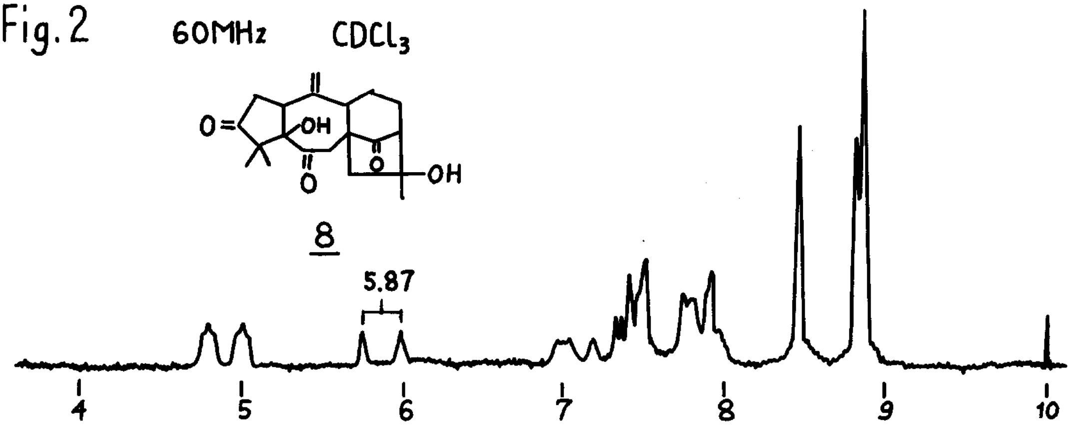


Fig. 2 60MHz $CDCl_3$



The A part of the AX spectrum due to the ——$COCH_3$-C≡C_3 system (Fig. 1) appears at an unusually low field (τ 6.42) and tridehydro G-II exhibits the corresponding doublet line at a still lower field (τ 5.87). These chemical shift values are reasonably accounted for only if the B ring adopts (as shown in 9 and 10) a twist chair form with C-1 as the axis carbon. There are then only two possibilities[5)] for the mode of fusion of the ring A, viz. two cis forms as shown by 9 and 10. Of these, only 9 is compatible with the observed long range coupling of the terminal methylene proton with C-1 proton in the n m r spectrum of tridehydro G-II (Fig. 2).

G-I and G-II readily form monoanhydroacetonides[3)] 11 and 12 respectively. Since the C-5 hydroxyl group of Gs is necessarily β oriented and can be

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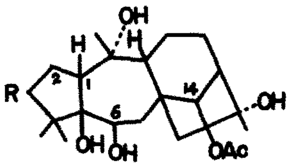
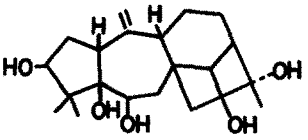
* The assignment was confirmed by double resonance.



1 R=--OH

1 R=∼OH



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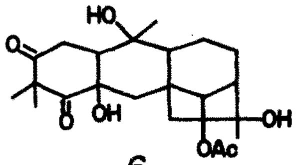

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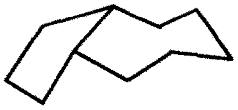

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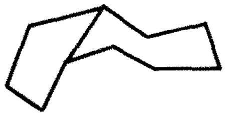

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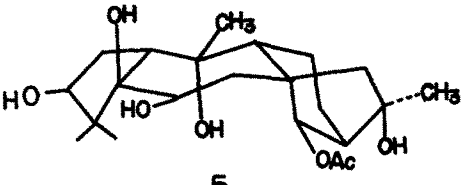

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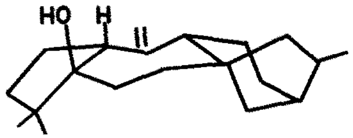

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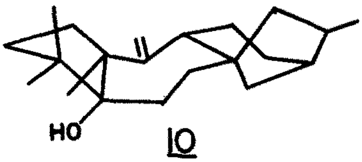

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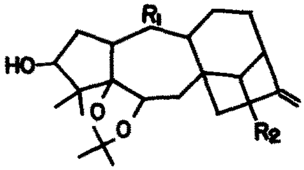
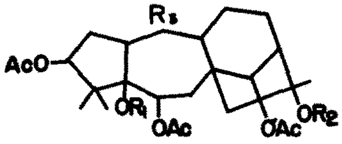


11 $R_1 = <^{CH_3}_{OH}$ $R_2 = OAc$

12 $R_1 = {=}CH_2$ $R_2 = OH$



13 $R_1 = Ac$ $R_2 = H$ $R_3 = <^{CH_3}_{OH}$

14 $R_1 = H$ $R_2 = Ac$ $R_3 = <^{CH_3}_{OH}$

15 $R_1 = H$ $R_2 = Ac$ $R_3 = {=}CH_2$

connected in the cis perhydroazulene system 9 only to the vicinal β hydroxyl group through a five membered ring,5) the C-6 hydroxyl group is β oriented. The equatorial nature of the C-6 hydroxyl group is further confirmed by the persence of a free tert-hydroxyl (C-10) absorption band at 3600 cm^{-1} in CCl$_4$ solution of triacetyl G-I (14), which is absent in tetraacetyl G-II.

Triacetyl G-I has been considered to have the structure 13.6) However, comparison of the τ values of methyl signals of Gs and their derivatives (Table 1) clearly demonstrates that the structure should be revised to 14 and tetraacetyl G-II is represented by 15. Ready acetylation of the C-15 tertiary hydroxyl group suggests the C-14 OAc/C-15 OH cis configuration of G-I. The IR spectrum in dilute CCl_4 solution of anhydro G-I acetonide 11 exhibits absorption bands at 3616 cm^{-1} and 3548 cm^{-1} in the hydroxyl group region. Since the C-10 hydroxyl group should not form an intramolecular hydrogen bond (vide supra), the only cause for the latter absorption band is the hydrogen bond between the C-3 hydroxyl group and C-5 ethereal oxygen atom. Thus, the C-3 OH/C-5 OH cis relationship is demonstrated. Since (-) phenylbutyric acid was obtained in 29% optical yield on application of the Horeau's method7) to anhydro G-I acetonide, the absolute configuration 5 was concluded for G-I. The type 3 conformation of non-flexible acetonides of this absolute configuration requires that 3-dehydroanhydro G-I acetonide $C_{25}H_{36}O_6$ (m.p. 200-203°) should exhibit a negative Cotton effect. In fact, a value -130 was obtained for this compound in methanol solution.

Table 1. values of methyl signals of grayanotoxin derivatives in $CDCl_3$

		C-4 CH_3	C-10 CH_3	C-15 CH_3
Triacetyl G-I	(18)	9.08, 8.93	8.67	8.40
Tetraacetyl G-II	(19)	9.08, 9.08	——	8.38
Didehydro G-I	(7)	9.01, 8.96	8.65	8.60

REFERENCES

1) H. Kakisawa, T. Kozima, M. Yanai and K. Nakanishi, Tetrahedron 21, 3091 (1965).

2) W. H. Tallent, J. Org. Chem. 27, 2968 (1962); 29, 2756 (1964).

3) H. Meguri, J. Pharm. Soc. Japan 79, 1060 (1959).

4) Z. Kumazawa and R. Iriye, IUPAC Symposium on the Chemistry of Natural Products, Abstracts p. 43, Kyoto (1964).

5) J. B. Hendrickson, a) J. Am. Chem. Soc. 83, 4537 (1961); b) Tetrahedron 19, 1387 (1963).

6) H. Kakisawa, J. Chem. Soc. Japan 82, 1096, 1216 (1961).

7) A. Horeau and H. B. Kagan, Tetrahedron 20, 2431 (1964).