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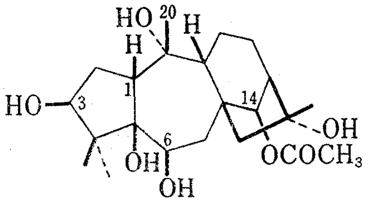
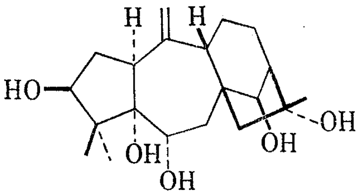
Stereochemistry of Grayanotoxins, Asebotoxins, and Rhodojaponins, Toxins of Ericaceae

The stereochemistry of the grayanotoxins, the poisonous constituents of a number of trees belonging to Ericaceae, has been the subject of protracted controversy in recent years and indeed presents an unresolved problem in diterpenoid chemistry. Thus, Kakisawa, *et al.*[1] proposed stereoformula I for grayanotoxin I (G–I), while Kumazawa and Irie[2] allotted a conflicting stereoformula II to G-II (desacetylanhydro G–I). Recently, Matsumoto, and Watanabe[3] reconfirmed the stereostructure I for G–I and further alleged that G–I exists in the conformation A. More recently, Kumazawa and Irie[4] and Iwasa and Nakamura[5] independently proposed the revised stereoformula III for G-II through a series of chemical transformation, respectively. Quite recently, Okuno and Matsumoto[6] still implied the A/B *cis* ring junction of the G's on the basis of the ORD evidence.



I



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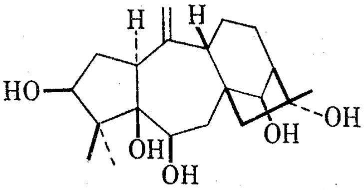
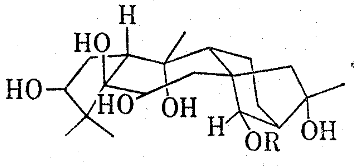


III



A

Meanwhile, we[7,8] have isolated the poisonous principles, asebotoxin I, II, and III (A-I, II, and III), and rhodojaponin I, II, and III (R-I, II, and III) from *Pieris japonica* D. Don

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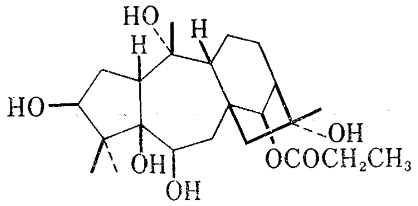
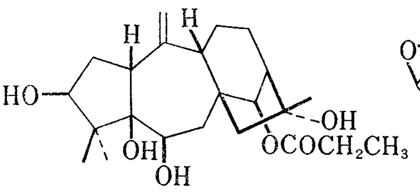
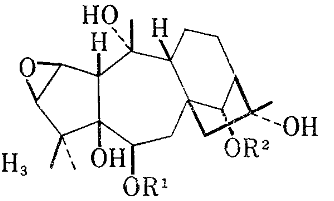
1) H. Kakisawa, T. Kozima, M. Yanai, and K. Nakanishi, *Tetrahedron*, **21**, 3091 (1965).
2) Z. Kumazawa and R. Irie, Abstract of the IUPAC Symposium on the Chemistry of Natural Productt, p. 43, Kyoto, April 1964.
3) T. Matsumoto and M. Watanabe, *Tetrahedron Letters*, **1968**, 6019.
4) Z. Kumazawa and R. Irie, Abstract of the Annual Meeting of the Agricultural Chemical Society of Japan, p. 137, Tokyo, April 1969.
5) J. Iwasa and Y. Nakamura, Abstract of the Annual Meeting of the Agricultural Chemical Society of Japan, p. 164, Tokyo, April 1969; *idem*, *Tetrahedron Letters*, **1969**, 3973.
6) T. Okuno and T. Matsumoto, *Tetrahedron Letters*, **1969**, 4077.
7) H. Hikino, K. Ito, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 854 (1969).
8) H. Hikino, K. Ito, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1078 (1969).

and *Rhododendron japonicum* SURINGER (Ericaceae), respectively, and deduced their structures to be IV, V, VI, VII, VIII, and IX, respectively, the stereochemistry being tentatively assigned by adopting that proposed for G–I by Kakisawa, *et al.*¹⁾

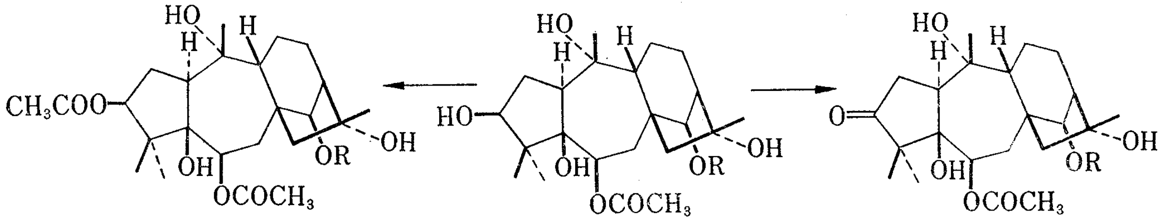

IV


V


VI : $R^1=H$, $R^2=COCH(OH)CH_3$
VII : $R^1=R^2=COCH_3$
VIII : $R^1=COCH_3$, $R^2=H$
IX : $R^1=R^2=H$

The stereochemistry of the G's is related to that of the A's and the R's on which we have been studying. Therefore, our interests caused us to re-examine the published evidence on the stereochemistry of the andromedane skeleton⁹⁾ from which all the known ericaceous toxins are derived. As a result, we concluded that all the stereochemical centers had been determined with the exception of C–1.

In order to clarify the C-1 configuration, the toxins have been subjected to a reinvestigation.


$R=COCH_2CH_3$ XI X XII

The splitting patterns of the C-1 hydrogen signals in the NMR spectra of A–I 6-acetate (X), A–I 3,6-diacetate (XI), and 3-dehydro A–I 6-acetate (XII)⁷⁾ which are dependent on the conformations of the A-rings are found identical (J=6, 10 Hz), demonstrating that these derivatives (X, XI, XII) adopt similar conformations in the A-rings. On the other hand, the ORD curve of 3-dehydro A–I 6-acetate (XII) indicates that the A-ring exists in a conformation so as to show a negative Cotton effect (a –69 for n–π^*). These results could not be rationalized in terms of the stereostructure IV or the conformation A for A-I. Further, we have recently observed that in the nuclear magnetic resonance (NMR) spectra of the R's, the coupling constants between the C–1 and C-2 hydrogens are *ca.* 1 Hz.⁸⁾ Although this value is very small, the proposal of a *cis* relationship between the C-1 and C-2 hydrogens is acceptable, if we take into account the fact that the vicinal coupling constants between the epoxide hydrogens and the hydrogens on adjacent carbon atoms in five–membered rings are generally much smaller than the values calculated from the Karplus equation with the dihedral angles measured on Dreiding models.¹⁰⁾ Consequently, the α-configuration of the C–1 hydrogen is suggested

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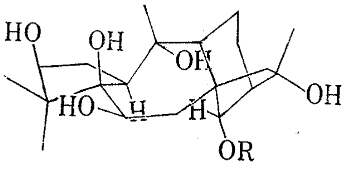
9) Although substantial investigations on these toxins have hitherto been performed, the general term for this rearranged kaurane skeleton has not been given. We now wish to propose the name andromedane for the parent hydrocarbon in memory of the substance andromedotoxin which was the first example isolated in a pure condition from this family but is now known as G-I.

10) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).

since the β-configuration of the 2,3-epoxide ring in the R-series has been shown by correlation with G–III.[8)]

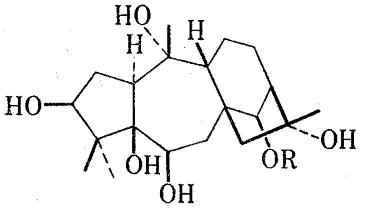
Since strong doubt has thus been raised concerned the validity of the proposed β-configuration of the C-1 hydrogen, further evidence to establish the C-1 configuration was sought. It was successful and the results will now be discussed.

If the C-1 hydrogen were α-oriented (*cf.* conformation B), 4σ-bond couplings may be observed between the C-1 and C-20 hydrogens since these hydrogens are situated in the relationship which satisfies the stereochemical requirement of this type of coupling (*i.e.* the W-arrangement). On the other hand, if the C-1 hydrogen were β-oriented (*cf.* conformation A), such couplings should not be observed. In fact, double resonance experiments have revealed that the A–I derivatives show appreciable 1,20-couplings. Furthermore, intramolecular nuclear Overhauser effects were observed between the C-1 and C-14 hydrogens in the A derivatives, demonstrating that these hydrogens are located in a spatially close relationship which is possible only when the C-1 hydrogen is in the α-configuration.

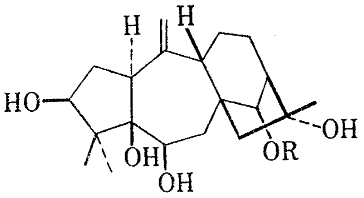


B

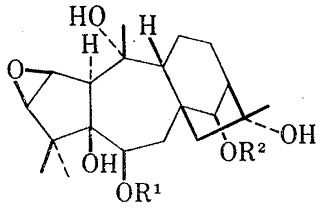
Whereupon it follows that the stereostructures of G–I, II, and III, A–I, II, and III, and R–I, II, and III must be revised as being as shown in formulae XIII, III, XIV, XV, XVI, XVII, XVIII, XIX, and XX, respectively.



XIII : $R=COCH_3$
XIV : $R=H$
XV : $R=COCH_2CH_3$



III : $R=H$
XVI : $R=COCH_2CH_3$



XVII : $R^1=H,\ R^2=COCH(OH)CH_3$
XVIII : $R^1=R^2=COCH_3$
XIX : $R^1=COCH_3,\ R^2=H$
XX : $R^1=R^2=H$

Further, a series of A–I congeners are concluded to adopt the conformation B from the splitting patterns of the C-1, C-3, and C-6 hydrogen signals, the intramolecular nuclear Overhauser effects between the C-1 and C-14 hydrogens in the NMR spectra of the A derivatives, and the ORD curve of the 3-one (XII) which shows a negative Cotton effect. Since, in the NMR spectra of the R derivatives, the coupling patterns of the C-6 hydrogens are similar to those in the A derivatives, and intramolecular nuclear Overhauser effects were observed between the C-1 and C-14 hydrogens, the R's are also considered to adopt a conformation similar to B.

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