

SPECIALIA

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Insect antifeedant terpenes, hot-tasting to humans

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Summary. Four dialdehyde sesquiterpenoids (1–4) isolated from East African *Warburgia* plants exhibit powerful antifeeding activity for larvae of the armyworms, *Spodoptera exempta* and *S. littoralis*. The hotness of these sesquiterpenes is associated with this activity. The specific absolute stereochemistry of these antifeedants appears to govern the hotness of the taste.

Products from the East African trees, *Warburgia ugandensis* and *W. stuhlmannii* (Canellaceae) are used often as food spices and medicine². The sesquiterpenes, polygodial (1)³, warburganal (2)⁴, muzigadial (3)⁵ and ugandensidial (4)⁶, isolated from the bark of these trees, are very hot to human taste. These hot principles, which are considered to be oxidation products of the drimenin skeleton, exhibit powerful antifeedant activity against larvae of the armyworms, *Spodoptera exempta* and *S. littoralis*. Interestingly, these 4 insect antifeedants taste very hot to humans, whereas 4 other non-active compounds (5–8), including epipolygodial, isolated from the same sources, are tasteless. A similar example is the bitter-tasting antifeedants of *Rabdosia* plants⁷.

There appears to be some systematic relationship between taste and the structural characteristics of the substances, but a definite correlation between these two has not yet been established, in spite of the tremendous efforts made by numerous investigators. We wish to describe herein a qualitative observation relating the hot taste to the antifeeding activity of 4 dialdehyde sesquiterpenes.

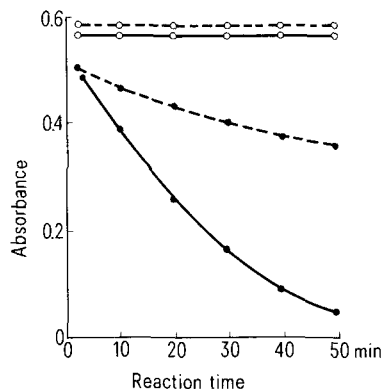
The simplest structure representative of the hot-tasting sesquiterpenoids, polygodial, was first isolated from the sprout of *Polygonum hydropiper*, a well known relish (meji-so in Japanese) for 'sashimi'⁸. Polygodial, which possesses a

β -aldehyde group at C-9, tastes very hot, whereas its epimer epipolygodial with an α -aldehyde moiety at C-9 is tasteless. This suggests that the enol moiety alone is not sufficient, and the C-9 aldehyde configuration is essential for hotness.

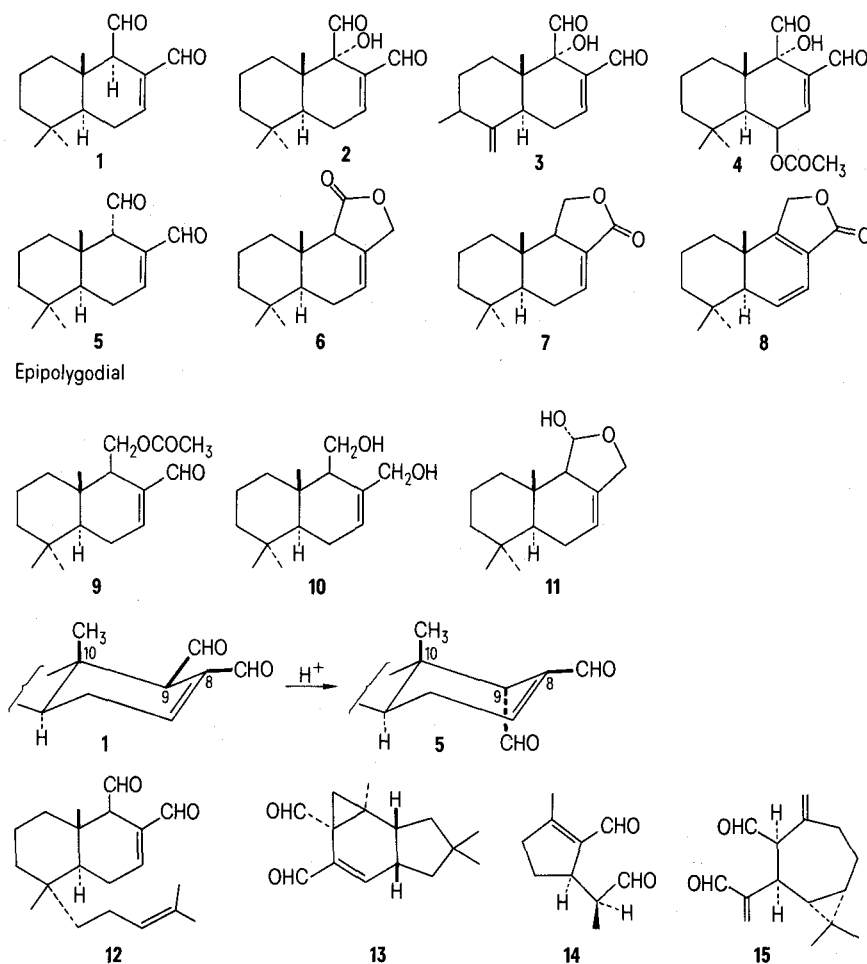
It should be noted that the C-9 equatorial aldehyde in polygodial is easily converted, under acidic condition, to the more stable axial epimer. This chemical conversion to epipolygodial seems to proceed through a keto-enol tautomerization followed by β -side protonation at sp^2 C-9 in the enol form. The preference of this β -protonation versus an α approach is probably due to the cause of an allylic strain⁹ resulting from dipole-dipole interaction of the 2 aldehyde groups when the C-9 aldehyde group is at the equatorial position. Therefore, this conformational preference reduces the interaction of the 2 vicinal aldehyde groups in epipolygodial.

Polygodial derivatives (9–11) all have similar chemical structures but, lacking the 'dialdehyde' moiety, they are not hot in taste and lack antifeedant activity. Therefore, the hotness of these compounds is essential for insect antifeedant activity. However, the mode of action of these compounds is still not clear, i.e., whether the antifeedant dialdehyde sesquiterpenoids act as an -SH acceptor, especially in view of the evidence for sulfhydryl groups in chemoreceptor membranes of insects^{10–13}. Although a biomimetic reaction of polygodial and epipolygodial with L-cysteine shows that polygodial reacts about 3 times faster in buffer solution at pH 9 than epipolygodial as shown in the figure, both sesquiterpenes have high reactivity with the sulfhydryl group, but the hot-tasting polygodial strongly suppresses the feeding response of *S. exempta* larvae whereas the non-tasting epipolygodial does not.

Electrophysiological observations imply that the action of polygodial and warburganal as feeding inhibitors for *S. exempta* involves an interference with the stimulus transduction process in chemoreceptor cells¹⁴. Polygodial seems to have the correct spatial geometry to form a complex with taste bud receptor sites, but epipolygodial does not. In other words, polygodial reveals the chiral nature of receptor organs by showing that a specific absolute stereochemistry is required to exhibit hotness. Warburganal, muzigadial and ugandensidial have molecular structures with the same chiral nature, but with additional groups, such as hydroxyl and acetoxyl groups. Modification of the A-ring also seems to have only a little effect on hotness. The present study suggests that only the functionality and stereochemistry of polygodial are necessary for the hot taste and other func-



Reactivity and change in absorbance of polygodial (4×10^{-5} M) — and epipolygodial (4×10^{-5} M) ---- (at 227 and 225 nm respectively) with (●) and without (○) cysteine (4×10^{-4} M) in pH 9 phosphate buffer. There was no reaction for either compound (with and without cysteine) in pH 7 phosphate buffer.



tional groups have little direct effect on the hot taste. Sacculatal (12), isolated as a pungent principle from a liverwort *Trichocoleopsis sacculata*, possesses an additional isoprene group¹⁵ when compared with polygodial.

The above hypothesis may not apply to all hot-tasting compounds, but it does effectively predict the hot taste in certain naturally occurring hot-tasting substances. For example isoverellal (13)¹⁶, hanegokedial (14)¹⁷ and dehydro-iridodial (15)¹⁸ possessing a similar enal-aldehyde moiety to that of polygodial are very hot to human taste¹⁹. To determine the hot taste, a 1-cm² filter paper was dipped into a 1% ethanol solution of each compound, air dried, and then tasted for hotness (pungency). In each case a group of 10 people were involved.

This finding suggests that the crucial criterion is probably the distance between the double bond end of the enal moiety and the nucleophilic dipole of the aldehyde, which is not part of the enal. It seems that in an enal-aldehyde system the fulfilment of this requirement would result in the interaction of the molecules with the active sites. Construction of the molecular structures by Dreiding stereomodels reveals that compound 14, with a fixed enal and rotating aldehyde groups, and compound 15, with a rotating enal and fixed aldehyde groups could adopt conformations which could meet the criterion of the enal-aldehyde system for hot taste.

Succulatal was provided by Dr. Y. Asakawa. This work was initiated during the stay of I.K. at the International Center of Insect Physiology and Ecology, Nairobi, Kenya. We also thank Mr A. Chapya for technical assistance.

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1 The authors are grateful to Proff. K. Nakanishi, A.S. Kende and T. Kubota for their interest and valuable discussion.