II was replaced with O-phosphoserine or serine.

A more detailed study of the enzyme(s) catalyzing the condensation reaction to form quisqualic acid is in progress in our laboratory. The biosynthetic pathway leading to the synthesis of 3,5-dioxo-1,2,4-oxadiazolidine ring has not been reported.

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Faculty of Pharmaceutical Sciences,
University of Chiba
1-33, Yayoi-cho, Chiba

Isamu Murakoshi
Fumio Kato
Joju Haginiwa

Faculty of Pharmaceutical Sciences,
Tohoku University
Aobayama, Sendai

Tsunematsu Takemoto

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Chemical Structure and Sweet Taste of Isocoumarins and Related Compounds

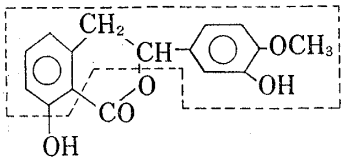
Phyllodulcin (the sweet principle of leaves of *Hydrangea serrata* Seringe var. *thunbergii*: Japanese name is Amacha) and its related compounds change into bitter or tasteless substances by a slight modification of its molecular structure.[1] There should be, therefore, a correlation between the sweet taste and the chemical structure of these compounds.

We have examined to elucidate the relationship between structure and appearance of sweet taste in this series of compounds and found that β-(3-hydroxy-4-methoxyphenyl) ethylbenzene (I, R, R′=H), which constitutes a partial structure of phyllodulcin indicated by a dotted line in the phyllodulcin structural formula is essential for the appearence of sweet taste[2] and that the number of methylene group between the two phenyl group is an important factor to the sweet taste. The existence of two methylene group brought the sweet taste strongly and the sweet taste has not appeared with either less or more methylene groups than that.[3] We have already reported the effect of substituents R and R′ in β-(3-hydroxy-4-methoxyphenyl) ethylbenzene derivatives I.[4]

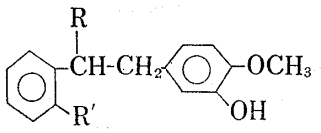
On the basis of these observations, we synthesized N-(3-hydroxy-4-methoxybenzyl)-aniline (II), a nitrogen analog of β-(3-hydroxy-4-methoxyphenyl) ethylbenzene from the point

1) Part I: M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, N. Yoshida, and T. Koyama, *Yakugaku Zasshi*, **92**, 367 (1972).
2) Part II: M. Yamato, K. Hashigaki, Y. Kuwano, and T. Koyama, *Yakugaku Zasshi*, **92**, 535 (1972).
3) Part III: M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, S. Murakami, and T. Koyama, *Yakugaku Zasshi*, **92**, 850 (1972).
4) Part IV: M. Yamato, K. Sato, K. Hashigaki, T. Ishikawa, and T. Koyama, *Yakugaku Zasshi*, **93**, 1639 (1973).

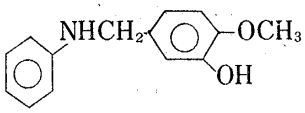
of view of theory of bioisosterism.[5] The compound (II) showed a fairly strong sweet taste, and the sweetness seemed to be superior to that of phyllodulcin or I.



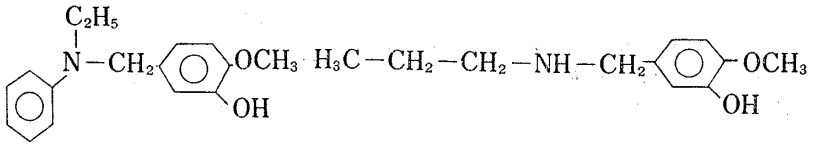
phyllodulcin



I



II



III IV

N-Ethyl-N-(3-hydroxy-4-methoxybenzyl)aniline (III) tasted bitter and this evidence agreed with the results reported earlier on I and its related compounds. As the phenyl group is considered to be equivalent with *n*-propyl group according to the theory of lipophilic equivalent,[6] we synthesized N-(3-hydroxy-4-methoxybenzyl)propylamine (IV). However, IV was found to be tasteless. This fact does not agree with the theory of lipophilic equivalent but rather indicated that the phenyl group in II might contribute to the bonding of this whole molecule with the sweet taste receptor by the Van der Waals force.

Faculty of Pharmaceutical Sciences,
Medical School, University of Okayama
Tsushima, Okayama-shi

MASATOSHI YAMATO
KOICHI SATO
KUNIKO HASHIGAKI
MIYOKO OKI
TAKAJI KOYAMA

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5) H.L. Friedam, "Influence of Isosteric Replacement upon Biological Activity," in First Symposium on Chemical-Biological Correlation (May 26—27, 1950), National Academy of Sciences—National Reserch Council, Washington, D.C., 1951, pp. 295—358.
6) H.G. Grimm, *Z. Electrochem.*, 31, 474 (1925); *idem*, *Naturwiss*, 17, 557 (1929).