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Chemical Structure and Sweet Taste of Isocoumarin and Related Compounds. VI[1]

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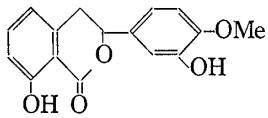
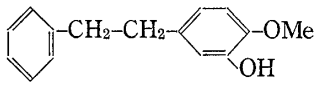
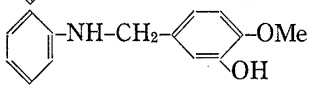
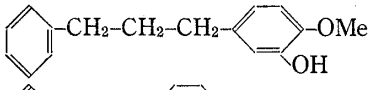
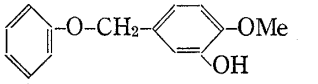
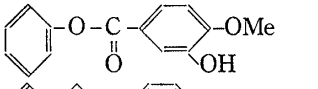
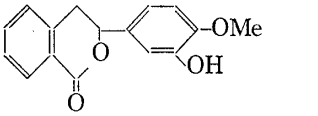
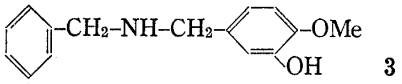
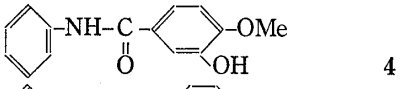
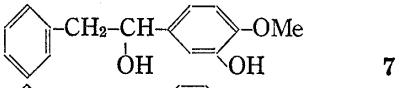
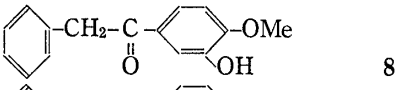
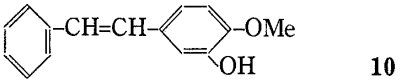
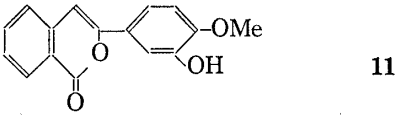
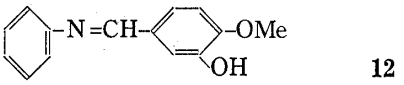
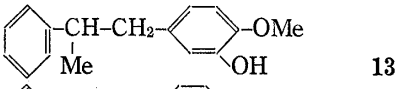
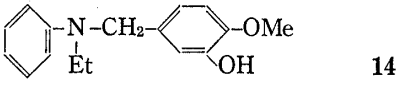
Structural modification of the ethylene moiety (**B**-moiety) of β-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**), which constitute an essential part of phyllodulcin molecule, was attempted to make the relationship between structure and sweet taste clearer, and compounds (**3**), (**4**), (**5**), (**6**), (**7**), and (**8**) were synthesized. The compound (**5**) had strong sweet taste, **6** had faint sweet taste and **3**, **4**, **7**, and **8** were tasteless.

On the base of these data, the taste of these compound was discussed in the connection with the favored conformation of them.

In our previous study[3] on the relationship between the structure and sweet taste of phyllodulcin, it was proposed that β-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**) may be the essential part to sweetness of phyllodulcin. The study was continued in order to make this

Table I

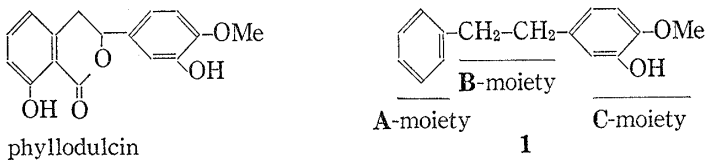
Compound		Taste
	phyllodulcin	sweet
	**1**	sweet[3]
	**2**	sweet[1]
		faint[4] sweet taste
	**5**	sweet
	**6**	faint sweet taste
	**9**	sweet[3]

Compound		Taste
	**3**	tasteless
	**4**	tasteless
	**7**	tasteless
	**8**	tasteless
	**10**	tasteless[3]
	**11**	tasteless[3]
	**12**	tasteless[1]
	**13**	tasteless[6]
	**14**	tasteless[1]

1) Part V: M. Yamato, K. Satō, K. Hashigaki, T. Ishikawa, M. Ôki, and T. Koyama, *Yakugaku Zasshi*, **94**, 359 (1974).
2) Location: *Tsushima-naka 1-1-1, Okayama 700, Japan.*
3) Part II: M. Yamato, K. Hashigaki, Y. Kuwano, and T. Koyama, *Yakugaku Zasshi*, **92**, 538 (1972).

relationship clearer and a bioisoster of **1**, 3-hydroxy-4-methoxybenzylaniline (**2**)[1] in which a methylene group of **1** is replaced by an imino group, revealed sweet taste.

In our present study of the molecular modification of **1**, the structure of **1** is divided for convenience into three parts, that is, the phenyl group (**A**-moiety), the ethylene group (**B**-moiety), and the 3-hydroxy-4-methoxyphenylgroup (**C**-moiety). In this paper, we describe the result of the modification of B-moiety (showed in Fig. 1).



phyllodulcin **1**

Fig. 1

N-(3-Hydroxy-4-methoxybenzyl)benzylamine (**3**), a homolog of **2**, was synthesized and proved to be tasteless. This fact agreed with the fact that the homolog of **1**, γ-(3-hydroxy-4-methoxyphenyl)propylbenzene,[4] revealed only faint sweet taste.

3-Hydroxy-4-methoxybenzanilide (**4**), in which a methylene group of **2** is replaced by a carbonyl group, was synthesized by debenzylation of 3-benzyloxy-4-methoxybenzanilide which was prepared from *O*-benzylisovanillic acid[5] and aniline. The amide (**4**) was tasteless.

3-Hydroxy-4-methoxybenzyl phenyl ether (**5**), in which a methylene group of **1** is replaced by an oxygen atom, was synthesized by the way shown in Chart 1. The Bayer-Villiger reaction of 2-methoxy-5-phenoxymethylacetophenone in the route (A) was unsuccessful because the content of flask exploded during evaporation of the solvent. Therefore, the route (B) was tried and gave the expected product (**5**). The compound (**5**) had excellent sweet taste.

Phenyl 3-hydroxy-4-methoxybenzoate (**6**), in which a methylene group of **5** is replaced by a carbonyl group, was synthesized by catalytic debenzylation of phenyl 3-benzyloxy-4-methoxybenzoate which is prepared by the reaction of *O*-benzylisovanillic acid and phenol with dicyclohexylcarbodiimide (DCC). The ester (**6**) revealed temporarily faint sweet taste.

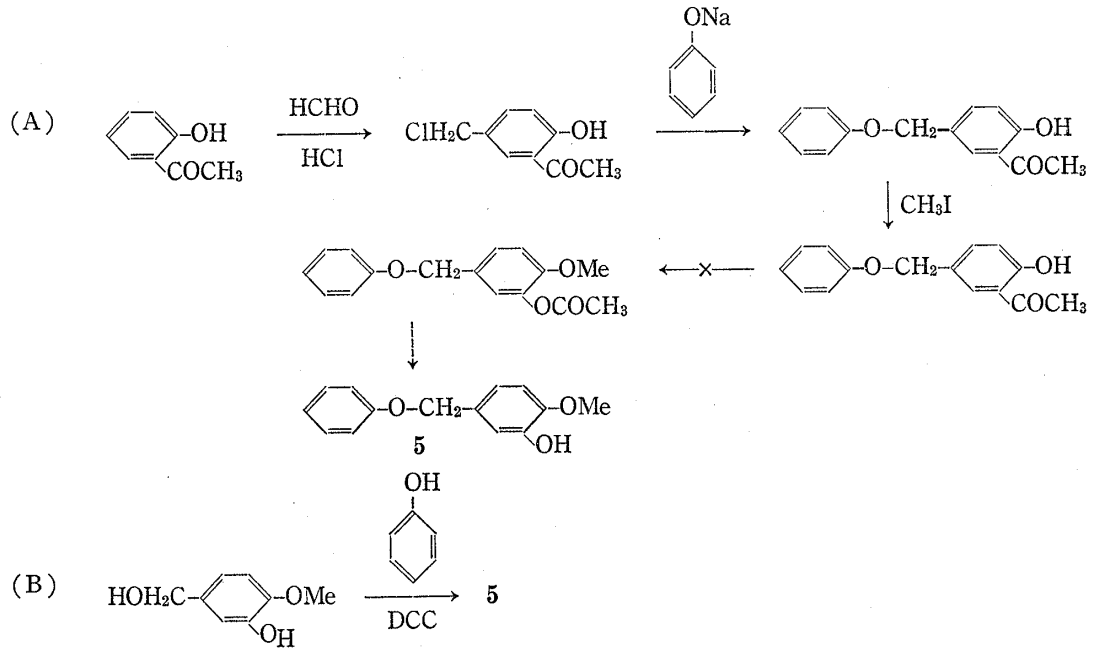


Chart 1

4) Part III: M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, S. Murakami, and T. Koyama, *Yakugaku Zasshi*, **92**, 850 (1972).
5) A. Lovercy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, **1930**, 817.

1-(3-Hydroxy-4-methoxyphenyl)-2-phenylethanol (**7**), in which a methylene group of **1** is substituted with a carbinol group, was obtained by debenzylation of 1-(3-benzyloxy-4-methoxyphenyl)-2-phenylethanol which is synthesized by Grignard reaction of *O*-benzylisovanillin and benzylmagnesium chloride. The hydroxy compound (**7**) thus obtained was tasteless.

3-Hydroxy-4-methoxyphenyl benzyl ketone (**8**) in which a methylene group of **1** is substituted with a carbonyl group was obtained by oxidation of 1-(3-benzyloxy-4-methoxyphenyl)-2-phenylethanol with chromic acid followed by debenzylation by heating with concentrated hydrochloric acid in acetic acid. The ketone (**8**) proved to be tasteless.

From these results of modification of *B*-moiety, following fact were known that the compounds in which a methylene group of **1** is replaced by an oxygen atom or by an imino group, that is, **2** and **5** behave as bioisosters of **1** and reveal excellent sweet taste, while the compounds in which a methylene group of **1**, **2**, or **5** is replaced by a carbonyl group, that is, the amide (**4**) and the ketone (**8**) are tasteless and the ester (**6**) reveal faint sweet taste.

On the basis of these facts, the consideration to the relationship between the structure and sweet taste leads to a assumption that the steric forms of these compounds are great important factor in the binding interaction with the receptor.

In the previous paper, following data were reported, that is, *β*-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**), 3-(3-hydroxy-4-methoxy)-3,4-dihydroisocoumarin (**9**),[3] and 3-hydroxy-4-methoxybenzylaniline (**2**) reveal sweet taste, but 3-hydroxy-4-methoxystilibene (**10**),[3] 3-(3-hydroxy-4-methoxyphenyl)isocoumarin (**11**),[3] and 3-hydroxy-4-methoxybenzylideneaniline (**12**)[1] are tasteless. These results suggested that the existence of double bond in **B**-moiety results in the loss of sweet taste because the planar configuration of the double bond and the restriction of free rotation of the chain would make the molecule unfit to the site of sweet taste receptor. *β*-(3-Hydroxy-4-methoxyphenyl)-*α*-methylethylbenzene (**13**)[6] and *N*-ethyl-*N*-(3-hydroxy-4-methoxybenzyl)aniline (**14**)[1] are tasteless, although, *β*-(3-hydroxy-4-methoxy)ethylbenzene (**1**) and 3-hydroxy-4-methoxybenzylaniline (**2**) reveal sweet taste. These results suggested that the alternation of the practical conformation of these compounds by introduction of *α*-substituents in **B**-moiety of essentially sweet compounds may result in the wrong form to combine with the sweet receptor.

In our present study, the reason of the data of turning the taste from sweet to tasteless by replacement a methylene group of **1**, **2**, and **5** by a carbonyl group to **4**, **6**, and **8** may be considered similarly as follows, that is, the configuration of the **B**-moiety of amide (**4**), ester (**6**), and ketone (**8**) may favor a planar configuration owing to resonance contribution of formula in which a double bond occupies (as shown in Fig. 2). Also, in the case of **7**, which is correspond to *β*-hydroxy derivative of **1**, it doesn't reveal sweet taste. The reason may be similar to that of **13** or **14**.

The further relationship between the conformation and sweet taste will be elucidate in the near future.

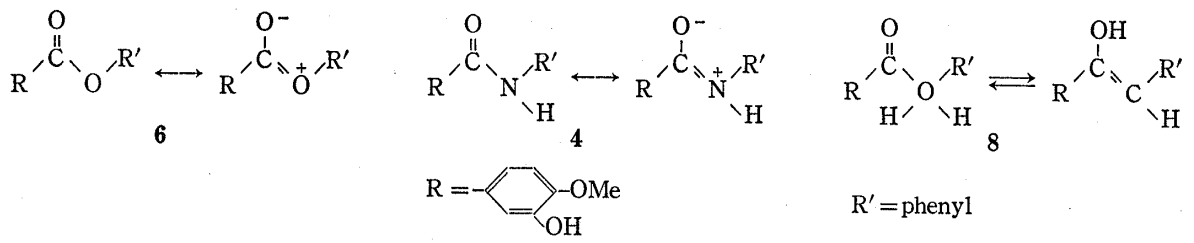


Fig. 2

6) Part IV: M. Yamato, K. Sato, K. Hashigaki, T. Ishikawa, and T. Koyama, *Yakugaku Zasshi*, **93**, 1639 (1973).

Experimental[7]

N-(3-Hydroxy-4-methoxybenzyl)benzylamine (3)——A mixture of isovanillin (3 g), benzylamine (3 g), and triethylamine (2 ml) in 20 ml of EtOH was refluxed for 6 hr, and reduced with H_2 in the presence of 20% Pd-C (0.05 g). After the completion of H_2 absorption, the solvent was evaporated. The residue was purified by column chromatography with silica-$CHCl_3$, and 0.3 g of 3 was obtained (6.4%). mp 58—60°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.35; H, 7.24; N, 5.50. NMR (solution in $CDCl_3$) δ: 3.24 (2H, s, broad, NH, OH), 3.70 (2H, s), 3.78 (2H, s) {[$NHCH_2$–$C_6H_3(OH)(OCH_3)$], ($NHCH_2Ph$)}, 3.85 (3H, s, OCH_3), 6.78—6.98 (3H, m, aromatic H), 7.34 (5H, m, aromatic H). Mass Spectrum *m/e*: 243 (M^+), 242 (M^+-1), 152 $[NHCH_2C_6H_3(OH)(OCH_3)]^+$, 137 $[CH_2C_6H_3(OH)(OCH_3)]^+$, 106 $(PhCH_2NH)^+$, 91 $(PhCH_2)^+$. Its ethanol solution is tasteless.

3-Hydroxy-4-methoxybenzanilide (4)——To a solution of 3-benzyloxy-4-methoxybenzoic acid (6.9 g), prepared from *O*-benzylisovanillin, in dry pyridine (12 ml), *p*-tosyl chloride was added and stirred for 5 min. Then, aniline (1.2 g) was dropped to the reactant and stirred at 50° for 6 hr. After the reaction, 5% NaOH (55 ml) and $NaHSO_3$ (2.6 g) was added, the yellowish precipitate was filtered off and the filtrate was extracted with ether. The ether layer was washed with H_2O and evaporated. The residue was recrystallized from MeOH–EtOH (2: 1) yielding 2.21 g of 3-benzyloxy-4-methoxybenzanilide (50.2%). mp 190—193°. NMR (solution in d_6-DMSO) δ: 3.85 (3H, s, OCH_3), 5.18 (2H, s, OCH_2Ph), 6.90—7.90 (13H, m, aromatic H), 10.06 (1H, s, NHCO).

This compound (2.21 g) was reduced with H_2 in the presence of 20% Pd-C catalyst in AcOH. After the solvent was evaporated and the residue was recrystallized from benzene and 0.81 g of **4** was obtained (50.3%). mp 215—217.5°. *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.20; H, 5.41; N, 5.81. NMR (solution in d_6-DMSO) δ: 3.84 (3H, s, OCH_3), 6.90—7.90 (8H, m, aromatic H), 10.1 (1H, s, NHCO). Mass Spectrum *m/e*: 243 (M^+), 151 $[OCC_6H_3(OH)(OCH_3)]^+$, 123$[C_6H_3(OH)(OCH_3)]^+$. Its ethanol solution is tasteless.

3-Hydroxy-4-methoxybenzyl Phenyl Ether (5)——A mixture of 3-hydroxy-4-methoxybenzyl alcohol[8] (3.7 g), obtained by reduction of isovanillin with $NaBH_4$, phenol (2.6 g), and DCC (4.0 g) was sealed in a tube and heated in an oil bath at 100—110° for 24 hr. The reaction mixture was cooled, the product was extracted with AcOEt. The solvent was evaporated, and the residue was purified by the column chromatography with silica-$CHCl_3$. The first fraction was recrystallized from EtOH to give 0.4 g of **5** (8.7%). mp 78—81°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.21; H, 6.09. NMR (solution in $CDCl_3$) δ: 3.86 (3H, s, OCH_3), 4.97 [2H, s, $OCH_2C_6H_3(OH)(OCH_3)$], 5.60 (1H, broad, OH), 6.75—7.11 (5H, m, aromatic H), 7.12—7.45 (3H, m, aromatic H). Mass Spectrum *m/e*: 230 (M^+), 137 $[CH_2C_6H_3(OH)(OCH_3)]^+$. Its ethanol solution reveal strong sweet taste.

Phenyl 3-Hydroxy-4-methoxybenzoate (6)——A solution of 3-benzyloxy-4-methoxybenzoic acid (5.3 g),[5] prepared from O-benzylisovanillin,[5] phenol (1.8 g), and DCC (4.5 g) in 20 ml of benzene was heated at 80° for 4 hr, the product was extracted with ether, the ether layer was washed with 5% $KHCO_3$ and H_2O, the solvent was removed and the residue was purified by column chromatography with silica-CH_2Cl_2. There was obtained 1.5 g of phenyl 3-benzyloxy-4-methoxybenzoate (22.7%). mp 125—127°.

This compound (1.5 g) was reduced in 50 ml of EtOH with H_2 in the presence of 10% Pd-C (0.2 g). After the completion of H_2 absorption, the solvent was evaporated, the residue was recrystallized from cyclohexane yielding 0.7 g of (6) (64.2%). mp 145—147°. *Anal.* Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.88; H, 4.93. NMR (solution in $CDCl_3$) δ: 3.95 (3H, s, OCH_3), 5.74 (1H, broad, OH), 6.75—7.90 (8H, m, aromatic H). Mass Spectrum *m/e*: 244 (M^+), 151 $[OC\text{-}C_6H_3(OH)(OCH_3)]^+$, 94 $(C_6H_5OH)^+$. Its ethanol solution reveal faint sweet taste.

1-(3-Hydroxy-4-methoxyphenyl)-2-phenylethanol (7)——The Grignard reagent was prepared by the reaction of benzyl chloride (23 g) with Mg (4.3 g) in 200 ml of dry ether. A solution of *O*-benzylisovanillin (34 g) in 200 ml of dry ether was added dropwise to the Grignard reagent and refluxed for 5 hr. The content was decomposed with ice-water, acidified with dil.H_2SO_4 and extracted with ether. The ether layer was evaporated, and the residue was recrystallized from cyclohexane. There was obtained 43 g of 1-(3-benzyloxy-4-methoxyphenyl)-2-phenylethanol (94.5%). mp 79—82°. NMR (solution in $CDCl_3$) δ: 1.55—2.00 (1H, broad, OH), 2.90 (2H, d, J=7.0 Hz, $CH_2C_6H_5$), 3.84 (3H, s, OCH_3), 4.78 (1H, t, J=7.0 Hz, CH–OH), 5.11 (2H, s, $OCH_2C_6H_5$), 6.83—7.02 (3H, m, aromatic H), 7.02—7.55 (10H, m, aromatic H).

This compound was catalytically reduced in 100 ml of EtOH with 10% Pd-C (0.3 g). After the completion of H_2 absorption, the solvent was evaporated, the residue was recrystallized from ether yielding 1.3 g of (7) (89%). mp 111—112°. *Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.61; H, 6.74.

7) All melting points were measured on a micro hot-stage apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained on a Hitachi Model R-22 spectrometer at 90 MHz employing tetramethylsilane as an internal standard. Mass spectra were measured by a Shimadzu Model LKB-9000 spectrometer.

8) G. Lock, *Chem. Ber.*, **62**, 1181 (1929).

NMR (solution in d_6-acetone) δ: 2.93 (2H, d, J_1=7 Hz, $C\underline{H}_2C_6H_5$), 3.78 (3H, s, $OC\underline{H}_3$), 3.94 (1H, d, J_2=4 Hz, CH–O$\underline{H}$), 4.78 (1H, m, J_1=7 Hz, J_2=4 Hz, C$\underline{H}$–OH), 6.67—6.97 (3H, m, aromatic H), 7.22 (5H, singlet with shoulder, $CH_2C_6H_5$), 7.30 (1H, s, O$\underline{H}$). Mass Spectrum *m/e*: 244 (M^+), 226 (M^+-H_2O), 153 [$CHOH-C_6H_3(OH)(OCH_3)]^+$. Its ethanol solution is tasteless.

3-Hydroxy-4-methoxyphenyl Benzyl Ketone (**8**)——1-(3-Benzyloxy-4-methoxyphenyl)-2-phenylethanol (10 g) (described above) was added to a solution of $K_2Cr_2O_7$ (5 g), conc. H_2SO_4 (6 ml) and H_2O (100 ml), and heated at 50° for 1 hr with stirring. The reaction mixture was cooled, the precipitates was filtered off, and recrystallized from EtOH, yielding 8 g of 3-benzyloxy-4-methoxyphenyl benzyl ketone (80.3%). mp 105—106°. NMR (solution in $CDCl_3$) δ: 3.92 (3H, s, $OC\underline{H}_3$), 4.17 (2H, s, $COC\underline{H}_2$), 5.18 (2H, s, $OC\underline{H}_2Ph$), 6.80—7.84 (13H, m, aromatic H).

Two grams of this compound was dissolved in the mixture of conc. HCl (15 ml) and AcOH (30 ml) and heated at 70° for 1 hr. The reactant was poured into ice-water, and the precipitates was taken out filtration. Recrystallization of the product from dil. EtOH gave 1 g of **8** (69%). mp 106—107°. *Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.42; H, 5.90. NMR (solution in $CDCl_3$) δ: 3.91 (3H, s, $OC\underline{H}_3$), 4.20 (2H, s, $COCH_2$), 5.75 (1H, s, OH), 6.83—7.76 (8H, m, aromatic H). Mass Spectrum *m/e*: 242 (M^+), 151 [$CO-C_6H_3(OH)(OCH_3)]^+$. Its ethanol solution is tasteless.