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

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Structural modification of the 3-hydroxy-4-methoxyphenyl moiety (C moiety) of β-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**), which constitutes an essential part of phyllodulcin molecule, was attempted to clarify the relationship between the structure and sweet taste.

The 4-methoxyl group of **1** being replaced with higher homologous alkoxyl groups such as an ethoxyl and a propoxyl group, the level of sweetness of these homologs was found to decrease with increasing number of methylenes in the alkoxyl group.

β-(3-Hydroxy-4-methoxycyclohexyl)ethylcyclohexane (**8**) synthesized by reduction of both aromatic rings of **1** had a bitter taste.

Aliphatic derivatives of **1** corresponding to the structure with the aromatic ring of the C moiety opened at the dashed line through a and b as shown in Table II, **9**, **10**, **11**, **12**, **13**, **14**, and **15** were synthesized. All of these compounds had a bitter taste except tasteless **15**.

Keywords——phyllodulcin; isocoumarin; sweetness; structure-activity relationship; molecular modification; size of alkoxyl groups

Our study on the relationship between the structure and sweet taste of phyllodulcin was carried out by means of molecular modification of β-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**) which is the essential structure of sweet phyllodulcin.[3] In the molecular modification of **1**, its structure was divided into three parts; phenyl moiety (A moiety), ethylene moiety (B moiety), and 3-hydroxy-4-methoxyphenyl moiety (C moiety). The results of the modification of the B moiety was previously reported.[4]

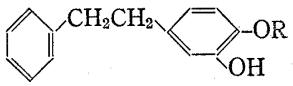
According to the molecular theory of sweet taste proposed by Schallenberger and Acree,[5] sweet compounds have commonly both acidic structure unit (AH) and basic unit (B) in their molecules, and the AH–B distance was found to be 2.5—4.0 Å. The sweet derivatives of isocoumarin and related compounds in our study seem to uphold this theory. For example, the hydroxyl and methoxyl groups in the C moiety of **1** may correspond to the AH and B unit of Schallenberger theory, respectively. However, it is known that this theory is not applicable in all the compounds. For instance, β-(4-hydroxy-3-methoxyphenyl)ethylbenzene (**2**) was tasteless,[6] in which a hydroxyl and a methoxyl group were introduced into the reversed position in the C moiety of **1**. This fact suggests that the presence of 3-hydroxyl and 4-methoxyl group is essential. In addition, it is evident, from a number of independent studies, that the sweet taste does not appear even when the structure of C moiety is essentially fulfilled unless the other moieties do not satisfy the requirement for attachment to the sweet receptor.

1) M. Yamato, K. Hashigaki, E. Honda, K. Sato, and T. Koyama, *Chem. Pharm. Bull.* (Tokyo), **25**, 695 (1977).
2) Location: *Tsushima-naka, 1-1-1, Okayama, 700, Japan.*
3) M. Yamato, K. Hashigaki, Y. Kuwano, and T. Koyama, *Yakugaku Zasshi*, **92**, 535 (1972).
4) M. Yamato, K. Hashigaki, J. Uenishi, I. Yamakawa, N. Sato, and T. Koyama, *Chem. Pharm. Bull.* (Tokyo), **23**, 3101 (1975).
5) R.S. Schallenberger and T.E. Acree, *Nature*, **216**, 480 (1967).
6) M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, N. Yoshida, and T. Koyama, *Yakugaku Zasshi*, **92**, 367 (1972).

In our study, modification of the C moiety was attempted to elucidate the relationship between the sweet taste and the structure of C moiety of **1**, without alteration of other moieties.

The acidic hydroxyl group at 3-position was replaced by a basic or an acidic group: β-(3-amino-4-methoxyphenyl)ethylbenzene (**3**) and 2-methoxy-5-phenethylphenoxyacetic acid (**4**) were synthesized and these were tasteless.

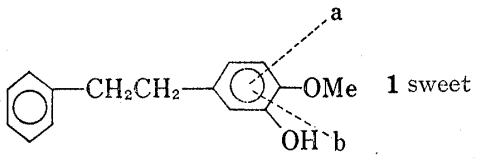
Table I. Relationship between the Alkyl Group and Sweet Taste

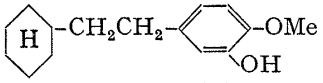
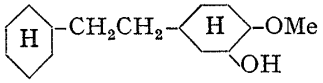


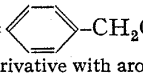
Compd. No.	R	Taste[a]
1	CH_3	sweet (×300)
5	CH_2CH_3	sweet (×1—10)
6	$CH_2CH_2CH_3$	tasteless

a) The sweetness of test sample was compared with that of sucrose. An aqueous ethanol solution of sucrose containing 3% was judged to be threshold level, and the sweet level of test samples was calculated from the concentration of test sample is required to attain the equivalent sweetness to that of 3% surosse solution.

Table II. Molecular Modification of C Moiety of **1**



Compd. No.	Formula[a]	Taste	
7		sweet	
8		bitter	
9	R–CH(CH3)CH2CH(OH)CH2OCH3	bitter	a[b]
10	R–CH2CH2CH(OH)CH2OCH3	bitter	a
11	R–CH2CH(OH)CH2OCH3	bitter	a
12	R–CH(CH3)CH2C(=O)CH2OCH3	bitter	a
13	R–CH(CH2CH2CH2OCH3)(CH2CH2OH)	bitter	b[c]
14	R–N(CH2CH2CH2OCH3)(CH2CH2OH)	bitter	b
15	R–N(CH2CH2CH2OCH3)(CH2COOH)	tasteless	b

a) R = 

b) a: derivative with aromatic ring opened at a (dashed line)
c) b: derivative with aromatic ring opened at b (dashed line)

As replacement of the 4-methoxyl group with higher homologous alkoxyl groups, ethoxyl and propoxyl derivatives were synthesized. Analogous study was made for the derivatives of dihydrochalcones,[7] and the sweet taste of these homologs was found to increase with the increasing number of methylenes in the alkokyl group. However, in our present work on isocoumarin derivatives, the order of sweet taste did not agree with that of dihydrochalcones, and the order was reversed, that is, the methoxyl derivative (**1**) was the sweetest, the ethoxyl derivative (**5**) was only faintly sweet, and the propoxyl derivative (**6**) was tasteless (Table I).

In our previous study,[8] β-(3-hydroxy-4-methoxyphenyl)ethylcyclohexane (**7**) was synthesized as the reduced product of the A moiety in **1** and it has a sweet taste. This time, as the reduced product of C moiety, β-(3-hydroxy-4-methoxycyclohexyl)ethylcyclohexane (**8**) was synthesized by catalytic reduction of both aromatic rings of **1** and this compound had a bitter taste. This fact seemed to be of interest.

In the course of the structural modification of the C moiety, aliphatic derivatives were synthesized, which correspond to the structure with the aromatic ring of the C moiety opened at the dashed line through a and b as shown in Table II. (5-Hydroxy-6-methoxy-3-

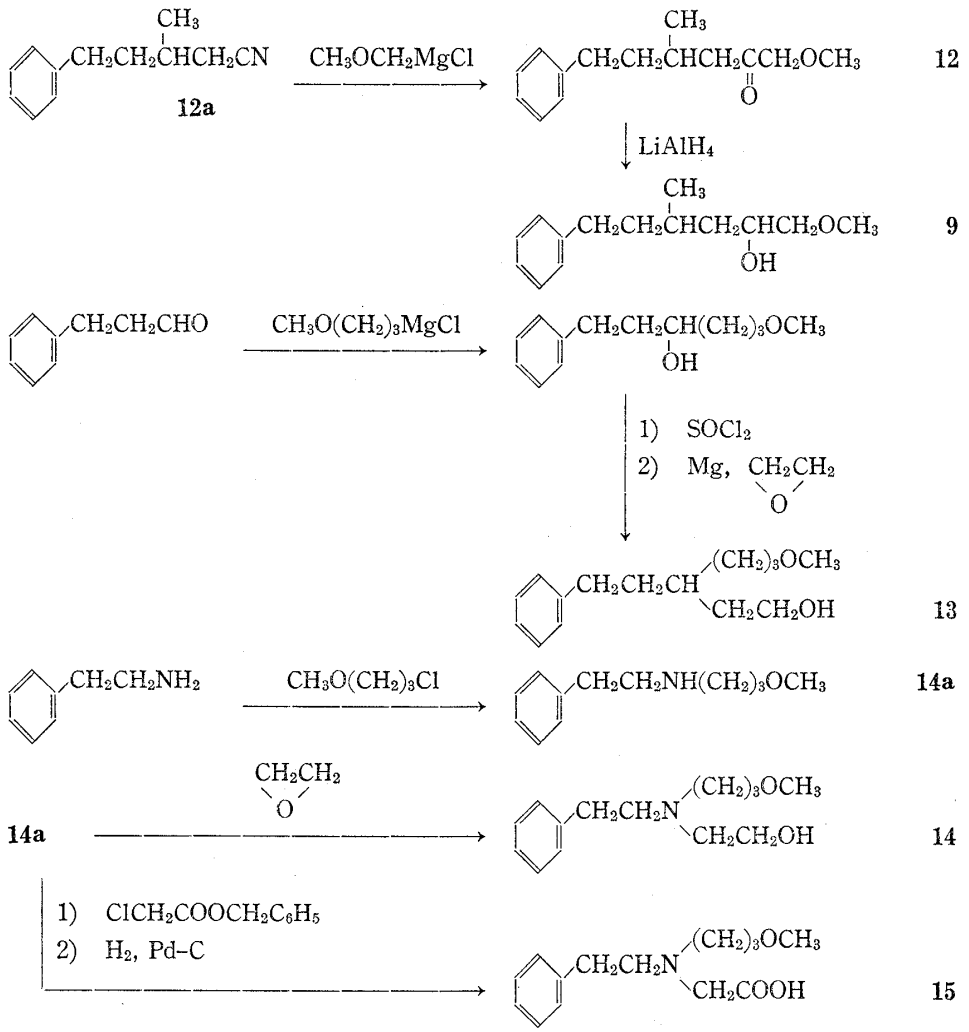


Chart 1

7) L. Krbeckek, G. Inglett, M. Holik, B. Dowling, R. Wagner, and R. Riter, *J. Agr. Food Chem.*, **16**, 109 (1968).
8) M. Yamato, T. Kitamura, K. Hashigaki, Y. Kuwano, S. Murakami, and T. Koyama, *Yakugaku Zasshi*, **92**, 850 (1972).

methylhexyl)benzene (**9**), (5-hydroxy-6-methoxyhexyl)benzene (**10**), (4-hydroxy-5-methoxypentyl)benzene (**11**), and (6-methoxy-3-methyl-5-oxohexyl)benzene (**12**) were synthesized and these compounds correspond to the derivatives with the aromatic ring opened at a (dashed line). The compounds **9**, **10**, **11**, and **12** had a bitter taste. (3-*β*-Hydroxyethyl-6-methoxyhexyl)benzene (**13**), which corresponds to the derivative with the aromatic ring opened at b (dashed line), *N*-(2-hydroxyethyl)-*N*-(3-methoxypropyl)phenethylamine (**14**), an *N*-analogue of **13**, and *N*-phenethyl-*N*-(3-methoxypropyl)glycine (**15**), expected to have an increased acidity, were synthesized (Chart 1). The compounds **13** and **14** had a bitter taste and **15** was tasteless.

The taste of these compounds (**8**—**14**) resulted in bitter, the aromatic group in C moiety of sweet compound **1** being changed to an aliphatic ring or chain. These facts seem reasonable to assume that the acidity of hydroxyl group or the basicity of methoxyl group and the conformation of the aliphatic derivatives differ from those of the sweet aromatic derivatives.

Experimental[9]

***β*-(3-Amino-4-methoxyphenyl)ethylbenzene** (**3**)——1) To a solution of 4-hydroxydibenzyl (11.8 g) in dry ether (140 ml) and dry benzene (140 ml), a mixed acid of HNO_3 (16.5 ml) and H_2SO_4 (11.0 ml) was added dropwise while cooling with ice-water. The solution was stirred at 10° for 2 hr, and further stirred at 30° for 3 hr. After cooling, the reaction mixture was washed with H_2O and the solvent was evaporated. The residue was purified by chromatography over silica gel and eluted with CH_2Cl_2 to give yellow needles of *β*-(4-hydroxy-3-nitrophenyl)ethylbenzene (**3a**) (12 g, 82.3%), mp 47—48°. NMR (in CCl_4) *δ*: 2.76 (4H, s, CH_2CH_2), 6.72—7.22 (7H, m, aromatic H), 7.68 (1H, d, $J=2$ Hz, C_2H), 10.14 (1H, s, OH). Mass Spectrum *m/e*: 243 (M^+), 152 ($M^+-CH_2C_6H_5$). 2) A mixture of **3a** (3.0 g), methyl iodide (10 ml), anhyd. K_2CO_3 (5.0 g), and dry acetone (30 ml) was refluxed until the reactant gave a negative reaction to the diazo test. The precipitate was filtered off, and the filtrate was concentrated. Recrystallization of the residue from cyclohexane gave *β*-(4-methoxy-3-nitrophenyl)ethylbenzene (**3b**) (2.5 g, 80.6%), mp 70—71°. NMR (in $CDCl_3$) *δ*: 2.90 (4H, s, CH_2CH_2), 3.91 (3H, s, OCH_3), 6.97 (1H, d, $J=9$ Hz, C_5H), 7.07—7.43 (6H, m, aromatic H), 7.64 (1H, d, $J=3$ Hz, C_2H). Mass Spectrum *m/e*: 257 (M^+). 3) A solution of **3b** (3.5 g) in EtOH (100 ml) was reduced over 5% Pd–C (0.3 g). After the completion of H_2 absorption, the solvent was removed, and the residue was recrystallized from cyclohexane to give **3** (2.0 g, 90.9%), mp 85—86°. NMR (in CCl_4) *δ*: 2.73 (4H, singlet with shoulder, CH_2CH_2), 3.55 (2H, singlet with shoulder, NH_2), 3.78 (3H, s, OCH_3), 6.30—6.45 (2H, m, aromatic H), 6.60 (1H, d, $J=9$ Hz, C_5H). 7.07 (5H, singlet with shoulder, aromatic H). Mass Spectrum *m/e*: 227 (M^+). Its ethanol solution is tasteless.

2-Methoxy-5-phenethylphenoxyacetic Acid (**4**)——A mixture of *β*-(3-hydroxy-4-methoxyphenyl)ethylbenzene (**1**)[3] (2.0 g), 33% NaOH (3.8 ml), and 50% chloroacetic acid (2.1 g) was refluxed for 11 hr, acidified with 10% H_2SO_4, and extracted with ether. The ether layer was extracted with 5% Na_2CO_3 and the Na_2CO_3 layer was acidified with 10% H_2SO_4 to give a precipitate. Recrystallization of the precipitate from benzene gave 0.4 g (16.2%) of **4**, mp 91—91.5°. NMR (in $CDCl_3$) *δ*: 2.84 (4H, s, CH_2CH_2), 3.83 (3H, s, OCH_3), 4.58 (2H, s, $C\underline{H}_2COOH$), 6.95—7.62 (5H, m, aromatic H). Mass Spectrum *m/e*: 286 (M^+). Its ethanol solution is tasteless.

***β*-(4-Ethoxy-3-hydroxyphenyl)ethylbenzene** (**5**)——1) *β*-(4-Ethoxy-3-nitrophenyl)ethylbenzene (**5a**) was prepared by the reaction of **3a** (12 g) with ethyl iodide (15.6 g) as described above for the synthesis of **3b**. A crude product thereby obtained was recrystallized from ligroin to give light yellow needles of **5a** (10.1 g, 75.4%), mp 53.5—55.5°. NMR (in $CDCl_3$) *δ*: 1.42 (3H, t, $J=7$ Hz, CH_3), 2.87 (4H, s, CH_2CH_2), 4.09 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 6.82—7.37 (7H, m, aromatic H), 7.55 (1H, d, $J=2$ Hz, C_2H). Mass Spectrum *m/e*: 271 (M^+). 2) A solution of **5a** (10 g) in EtOH was reduced over 5% Pd–C (0.5 g). After the completion of H_2 absorption, the solvent was evaporated, and the residue was recrystallized from cyclohexane to give 6.7 g (74.5%) of *β*-(3-amino-4-ethoxyphenyl)ethylbenzene (**5b**), mp 74—75°. *Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.64; H, 8.20; N, 5.84. NMR (in $CDCl_3$) *δ*: 1.38 (3H, t, $J=7$ Hz, CH_3), 2.80 (4H, s, CH_2CH_2), 3.38—3.82 (2H, broad singlet, NH_2), 3.98 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 6.37—6.78 (3H, m, C_2H, C_5H, and C_6H), 6.94—7.34 (5H, m, aromatic H). Mass Spectrum *m/e*: 241 (M^+). 3) To a diazonium solution of **5b** (6 g) prepared by the usual method, fluoroboric acid[10] was added. The resulting

9) All melting points were measured on a micro hot stage apparatus and are uncorrected. 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. IR spectra were obtained on a Nipponbunko Model DS-301 spectrometer.

10) E. Starky and D.T. Flood, "Organic Syntheses," Coll. Vol. II, ed. by John Wiley and Sons. Inc., New York, 1950, p. 225, 295.

precipitate of the diazoniumfluoroborate was filtered with suction, washed with H_2O and ether, and added into acetic acid (80 ml). The solution was refluxed for 9 hr until the reactant gave a negative reaction to the coupling test, poured into ice-water, and extracted with ether. After evaporation of the solvent, the residue was chromatographed over silica gel and eluted with CH_2Cl_2 to give **5** (2.31 g, 38.2%), which was recrystallized from ligroin, mp 50—52°. *Anal.* Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.14; H, 7.32. NMR (in $CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, CH_3), 2.80 (4H, s, $C\underline{H}_2C\underline{H}_2C_6H_5$), 4.02 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.34—5.69 (1H, broad singlet, OH), 6.45—6.78 (3H, m, aromatic H), 6.98—7.28 (5H, m, aromatic H). Mass Spectrum *m/e*: 242 (M^+). Its ethanol solution has a faint sweet taste.

β-(3-Hydroxy-4-*n*-propoxyphenyl)ethylbenzene (6)——1) β-(3-Nitro-4-*n*-propoxyphenyl)ethylbenzene (**6a**) was prepared by the reaction of **2a** (10.5 g) with *n*-propyl iodide (14.6 g) as described above for the synthesis of **3b**. A crude product thereby obtained was purified by chromatography over silica gel and eluted with CH_2Cl_2 to give an oil of **6a** (11.7 g, 95%). NMR (in $CDCl_3$) δ: 1.03 (3H, t, J=7 Hz, CH_3), 1.55—2.03 (2H, m, $C\underline{H}_2CH_3$), 2.89 (4H, s, $C\underline{H}_2C\underline{H}_2C_6H_5$), 4.00 (2H, t, J=6 Hz, OCH_2), 6.93 (1H, d, J=8 Hz, C_5H), 7.02—7.45 (6H, m, aromatic H), 7.59 (1H, d, J=2 Hz, C_2H). Mass Spectrum *m/e*: 285 (M^+). 2) **6a** (11 g) in EtOH was reduced over 5% Pd–C (0.5 g). After the completion of H_2 absorption, the solvent was evaporated, and the residue was recrystallized from ligroin to give β-(3-amino-4-*n*-propoxyphenyl)ethylbenzene (**6b**), (9.4 g, 95%), mp 38.5—40°. NMR (in $CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, CH_3), 1.55—1.94 (2H, m, $C\underline{H}_2CH_3$), 2.96 (4H, s, $C\underline{H}_2C\underline{H}_2C_6H_5$), 3.58 (2H, broad singlet, NH_2), 3.85 (2H, t, J=7 Hz, OCH_2), 6.33—6.64 (3H, m, aromatic H), 7.00—7.33 (5H, m, aromatic H). Mass Spectrum *m/e*: 255 (M^+). 3) A diazoniumfluoroborate of **6b** (9.2 g) prepared by the method as described above for the synthesis of **5**, was added into acetic acid, and the solution was refluxed for 12 hr. The reaction mixture was poured into ice-water and extracted with ether. Removal of the solvent gave a residue, which, after hydrolysis with NaOH, was neutralized with 10% H_2SO_4, and extracted with AcOEt. Removal of the solvent gave a residue which was chromatographed over silica gel and eluted with CH_2Cl_2 to give an oil of **6** (1.0 g, 10.6%). NMR (in CCl_4) δ: 0.96 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.20—1.89 (2H, m, $C\underline{H}_2CH_3$), 2.73 (4H, s, $C\underline{H}_2C\underline{H}_2C_6H_5$), 3.78 (2H, t, J=7 Hz, OCH_2), 5.26—5.62 (1H, broad singlet, OH), 6.33—7.22 (8H, m, aromatic H). Mass Spectrum *m/e*: 256 (M^+). Its ethanol solution is tasteless.

β-(3-Hydroxy-4-methoxycyclohexyl)ethylcyclohexane (8)——A solution of **1** (1.8 g) in acetic acid (40 ml) was reduced over Rh–Pt oxide (7: 3) (150 mg) prepared according to the direction of Nishimura[11] in an autoclave at a room temperature under 150 kg/cm² of hydrogen. After stirring for 30 min, the solvent was removed, and the residue was chromatographed over silica gel. The earlier elution with cyclohexane gave β-(3-hydroxy-4-methoxyphenyl)ethylcyclohexane[8] (200 mg) and next elution with benzene gave an oil of **8** (1.0 g, 52%). NMR (in $CDCl_3$) δ: 0.55—2.23 (22H, m, CH_2CH_2 and cyclohexyl H), 2.90—3.21 (1H, broad singlet, OH), 3.33 (3H, s, OCH_3), 3.35—3.61 (2H, m, C_3H and C_4H). Mass Spectrum *m/e*: 240 (M^+), 222 (M^+-H_2O). Its ethanol solution has a bitter taste.

(6-Methoxy-3-methyl-5-oxohexyl)benzene (12)——1) A mixture of benzylacetone (87.1 g), cyanoacetic acid (50.0 g), and ammonium acetate (1.8 g) was heated at 160—175° for 10 hr. The reaction mixture was extracted with AcOEt, and the solvent was evaporated. The residue was distilled under reduced pressure to give 65.7 g of an oil, bp 127—129° (4 mmHg). Mass Spectrum *m/e*: 171 (M^+). The oil was dissolved in EtOH (300 ml), and reduced over 10% Pd–C (0.7 g). After the completion of H_2 absorption, the solvent was removed and the residue was distilled under reduced pressure to give an oil of (4-cyano-3-methylbutyl)-benzene (**12a**), (56.7 g, 84.7%), bp 144—147° (8 mmHg). IR cm^{-1}: 2243 (CN). NMR (in CCl_4) δ: 1.07 (3H, d, J=6 Hz, CH_3), 1.45—1.95 (3H, m, C_2H and C_3H), 2.16 (2H, d, J=6 Hz, C_4H), 2.57 (2H, t, J=8 Hz, C_1H), 7.00—7.35 (5H, m, aromatic H). Mass Spectrum *m/e*: 173 (M^+). 2) A mixture of Mg (7.0 g), I_2 (a few crystals), and dry methylal (30 ml) was refluxed for 30 min in N_2 atmosphere, and further refluxed for 15 min after addition of $HgCl_2$ (a spatulaful). To the above mixture, a solution of **12a** (5.0 g) in methylal was added, and further freshly distilled chloromethyl methyl ether (23.5 g) was added dropwise for 2 hr at 0—5°. After stirring for 20 hr at 0—5°, the reaction mixture was acidified with NH_4Cl, and extracted with ether. The solvent was evaporated and the residue was chromatographed over silica gel. Elution with CH_2Cl_2 gave an oil which was distilled under reduced pressure to give 2 g (30.9%) of **12**, bp 150—155° (6 mmHg). NMR (in CCl_4) δ: 0.93 (3H, d, J=6 Hz, CH_3), 1.30—2.00 (3H, m, C_2H and C_3H), 2.25 (2H, d, J=6 Hz, C_4H), 2.51 (2H, t, J=7 Hz, C_1H), 3.25 (3H, s, OCH_3), 3.68 (2H, s, C_6H), 7.10 (5H, singlet with shoulder, aromatic H). IR cm^{-1}: 1704 (C=O). Mass Spectrum *m/e*: 220 (M^+), 202 (M^+-H_2O), 175 ($M^+-CH_2OCH_3$). Its ethanol solution has a bitter taste.

(5-Hydroxy-6-methoxy-3-methylhexyl)benzene (9)——To a mixture of $LiAlH_4$ (2.0 g) and ether (30 ml), a solution of **12** (4.0 g) in ether (10 ml) was added dropwise and the mixture was refluxed for 3 hr. After cooling, the content was acidified with 10% H_2SO_4 and extracted with ether. Removal of the solvent gave a residue which was distilled under reduced pressure to give **9** (3 g, 69%), bp 153—154° (6 mmHg). *Anal.* Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.55; H, 9.89. NMR (in CCl_4) δ: 0.97 (2H, d.d, J_1=6 Hz, J_2=3 Hz, CH_3), 1.05—1.92 (5H, m, C_2H, C_3H, and C_4H), 2.08 (1H, broad singlet, OH), 2.57 (2H,

11) S. Nishimura, *Bull. Chem, Soc. Japan*, 34, 1544 (1961).

triplet with shoulder, $J=7$ Hz, C_1H), 2.92—3.23 (2H, m, C_6H), 3.30 (3H, s, OCH_3), 3.50—3.85 (1H, m, C_5H), 7.13 (5H, s, aromatic H). Mass Spectrum *m/e*: 222 (M^+), 204 (M^+-H_2O). Its ethanol solution has a bitter taste.

(5-Hydroxy-6-methoxyhexyl)benzene (10)——The compound **10** was similarly prepared by the Grignard reaction of 5-phenylpentylaldehyde[12] (12 g) with chloromethyl methyl ether (12 g) as described above for the synthesis of **12**. A crude product thereby obtained was purified by chromatography over alumina and eluted with benzene. Distillation under reduced pressure gave an oil of **10** (2.5 g, 16.7%), bp 160—162° (6 mmHg). NMR (in CCl_4) δ: 1.18—1.84 (6H, m, C_2H, C_3H, and C_4H), 2.12 (1H, broad singlet, OH), 2.53 (2H, t, $J=8$ Hz, C_1H), 3.11 (2H, d, $J=3$ Hz, C_6H), 3.22 (3H, s, OCH_3), 3.10—3.52 (1H, m, C_5H), 7.07 (5H, s, aromatic H). Mass Spectrum *m/e*: 208 (M^+). Its ethanol solution has a bitter taste.

(4-Hydroxy-5-methoxypentyl)benzene (11)——The compound **11** was similarly prepared by the Grignard reaction of 4-phenylbutyraldehyde[12] (6 g) with chloromethyl methyl ether as described above for the synthesis of **12**. A crude product thereby obtained was purified by chromatography over alumina with benzene to give an oil of **11** (2 g, 25.8%). NMR (in CCl_4) δ: 1.17—1.88 (4H, m, C_2H and C_3H), 2.00—2.22 (1H, broad singlet, OH), 2.52 (2H, triplet with shoulder, C_1H), 3.12 (2H, d, $J=3$ Hz, C_5H), 3.25 (3H, s, OCH_3), 3.15—3.43 (1H, m, C_4H), 7.09 (5H, s, aromatic H). Mass Spectrum *m/e*: 194 (M^+). Its ethanol solution has a bitter taste.

(3-β-Hydroxyethyl-6-methoxyhexyl)benzene (13)——1) To a Grignard reagent of 4-methoxypropyl chloride prepared by the usual method, a solution of β-phenylpropionaldehyde (25 g) in ether (50 ml) was added dropwise and the reaction mixture was refluxed for 3 hr. The content was acidified with 10% H_2SO_4, and extracted with ether. Removal of the solvent gave a residue which was distilled under reduced pressure to give 27 g (79.1%) of (3-hydroxy-6-methoxyhexyl)benzene (**13a**), bp 125—130° (5 mmHg). NMR (in CCl_4) δ: 1.25—1.87 (6H, m, C_2H, C_4H, and C_5H), 2.20—2.95 (2H, m, C_1H), 3.20 (3H, s, OCH_3), 3.27 (2H, t, $J=5$ Hz, C_6H), 3.18—3.65 (1H, m, C_3H), 7.12 (5H, s, aromatic H). 2) To a solution of **13a** (27 g), dry pyridine (3 drops), and dry benzene (30 ml), thionyl chloride (20 g) was added for 10 min at 0—5°. The reaction mixture was refluxed for 30 min, concentrated, and extracted with benzene. The solvent was evaporated and the residue was distilled under reduced pressure to give 13 g of an oil of (3-chloro-6-methoxyhexyl)benzene (**13b**), bp 115—120° (5 mmHg). NMR (in CCl_4) δ: 0.95—2.08 (6H, m, C_2H, C_4H, and C_5H), 2.23—2.68 (2H, triplet with shoulder, C_1H), 3.20 (3H, s, OCH_3), 3.15—3.80 (3H, m, C_3H and C_6H), 7.12 (5H, s, aromatic H). 3) To a Grignard reagent of **13b** (20 g) prepared by the usual method, a solution of ethylene oxide (3.7 g) in dry benzene (50 ml) was added dropwise. The reaction mixture was refluxed for 2 hr, acidified with 10% H_2SO_4, and extracted with ether. The solvent was evaporated, the residue was chromatographed over alumina and eluted with benzene to give an oil of **13**, which was distilled under reduced pressure, yield 4 g (20%), bp 160—162° (2 mmHg). NMR (in CCl_4) δ: 0.97—1.82 (9H, m, C_2H, C_3H, C_4H, C_5H, and $C\underline{H}_2CH_2OH$), 2.42—2.62 (2H, m, C_1H), 2.63 (1H, broad singlet, OH), 3.23 (3H, s, OCH_3), 2.80—3.35 (2H, m, $C\underline{H}_2OH$), 3.45 (2H, t, $J=6$ Hz, C_6H), 7.11 (5H, s, aromatic H). Mass Spectrum *m/e*: 236 (M^+). Its ethanol solution has a bitter taste.

***N*-(2-Hydroxyethyl)-*N*-(3-methoxypropyl)phenethylamine (14)**——1) A solution of β-phenethylamine (14 g) and 3-methoxypropyl bromide (19.5 g) in dry benzene (150 ml) was refluxed for 13 hr and extracted with 10% H_2SO_4. The H_2SO_4 layer was neutralized with 10% NaOH, and extracted with ether. Removal of the solvent gave a residue which was distilled under reduced pressure to give 6.0 g of an oil of *N*-(3-methoxypropyl)phenethylamine (**14a**), bp 140—142° (10 mmHg). NMR (in CCl_4) δ: 0.85 (1H, s, NH), 1.42—1.75 (2H, m, $C\underline{H}_2CH_2OCH_3$), 2.33—2.87 (6H, m, $C_6H_5C\underline{H}_2C\underline{H}_2NHC\underline{H}_2$), 3.17 (3H, s, OCH_3), 3.25 (2H, t, $J=6$ Hz, $C\underline{H}_2OCH_3$), 7.13 (5H, s, aromatic H). 2) A solution of **14a** (3 g) and ethylene oxide (1.5 g) in dry benzene (30 ml) was sealed in a tube and heated in an oil bath at 120° for 4 hr. The product was extracted with ether, and the ether layer was extracted with 10% H_2SO_4. The H_2SO_4 layer was neutralized with 10% KOH and extracted with ether. Removal of the solvent gave a residue which was chromatographed over alumina and eluted with benzene–petr. ether (1 : 1) to give an oil of **14** (0.8 g, 22.2%). NMR (in CCl_4) δ: 1.32—1.78 (2H, m, $C\underline{H}_2CH_2OCH_3$), 2.40 (1H, broad singlet, OH), 2.42—2.78 (8H, m, $C_6H_5C\underline{H}_2C\underline{H}_2NC\underline{H}_2$ and $C\underline{H}_2CH_2OH$), 3.20 (3H, s, OCH_3), 3.20 (2H, t, J=6Hz, $C\underline{H}_2OCH_3$), 3.35 (2H, t, $J=6$ Hz, $C\underline{H}_2OH$), 7.13 (5H, s, aromatic H). Mass Spectrum *m/e*: 237 (M^+). Its ethanol solution has a bitter taste.

***N*-Phenethyl-*N*-(3-methoxypropyl)glycine (15)**——A solution of **14a** (5.5 g) and benzyl α-chloroacetate (6.4 g) in dry benzene (100 ml) was refluxed for 3 hr, extracted with ether. Removal of the solvent gave a paste, which was used without further purification. The solution of the paste in EtOH was reduced over 10% Pd–C. After the completion of H_2 absorption, the solvent was removed. The residue was recrystallized from acetone to give **15** (2.5 g, 30.6%), mp 102—104°. *Anal.* Calcd. for $C_{14}H_{21}O_3N$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.45; H, 8.27; N, 5.64. NMR (in $CDCl_3$) δ: 1.66—2.10 (2H, m, $C\underline{H}_2CH_2OCH_3$), 2.63—3.31 (6H, m, $C_6H_5C\underline{H}_2C\underline{H}_2NC\underline{H}_2$), 3.28 (3H, s, OCH_3), 3.40 (2H, t, $J=6$ Hz, $C\underline{H}_2OCH_3$), 3.53 (2H, s, $C\underline{H}_2COOH$), 7.28 (5H, singlet with shoulder, aromatic H), 7.48 (1H, broad singlet, COOH). Mass Spectrum *m/e*: 251 (M^+), 206 (M^+-COOH). Its ethanol solution is tasteless.

12) J.V. Braun and O. Kruber, *Chem. Ber.*, **45**, 399 (1912).