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An Intensely Sweet Analogue of Phyllodulcin: 2-(3-Hydroxy-4-methoxyphenyl)-1,3-benzodioxan

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2-(3-Hydroxy-4-methoxyphenyl)-1,3-benzodioxan, an easily prepared acetal of *o*-hydroxybenzyl alcohol (salicyl alcohol) and 3-hydroxy-4-methoxybenzaldehyde (isovanillin), mimics the structure and taste of phyllodulcin, a rare, intensely sweet isocoumarin derivative. Preliminary tests indicate a 2 mg % solution of the new acetal to be approximately isosweet with a 6% sucrose solution, but it is slowly hydrolyzed in water with loss of sweetness.

The present controversy over the healthfulness of dietary sweeteners underscores the need for a harmless, noncariogenic, intensely sweet, additive for dietary foods and pharmaceuticals. Some naturally sweet products of botanical origin, or derivatives prepared from such extracted products, are known to have saccharin-like sweetness (Hodge and Inglett, 1974), but candidate compounds often have structures too complex for facile synthesis and are not isolated economically from agricultural sources. These limitations make it unlikely that a sweetener such as phyllodulcin (1, Arakawa and Nakazaki, 1959; Asahina and Asano, 1931), an isocoumarin derivative isolated from *Hydrangea thunbergii Sieb.* and consumed as a tea-like decoction in Japan will be of commercial value, even though it is reported to be either 400 (Yamato et al., 1977) or 600–800 times sweeter than sucrose (Suzuki et al., 1977). A more likely source of suitable sweeteners will be easily prepared, harmless, synthetic compounds which contain the specific structural features required for expression of sweetness in the natural model. One such compound is **2**, the acetal of 3-hydroxy-4-methoxybenzaldehyde (**4**) and *o*-hydroxybenzyl alcohol (**7**), which mimics the taste of phyllodulcin and contains some of its structural features.

RESULTS AND DISCUSSION

Synthesis of the sweet acetal, 2-(3-hydroxy-4-methoxyphenyl)-1,3-benzodioxan (**2**) is straightforward, offering

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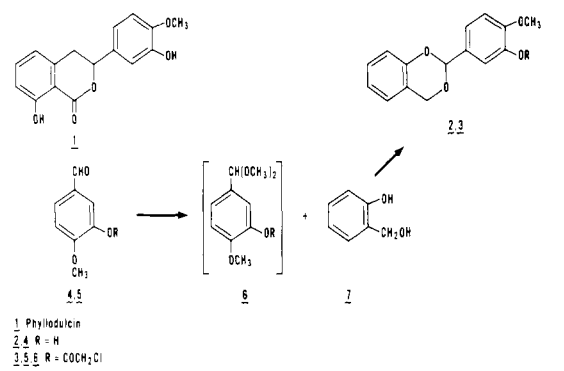
Scheme I



overall yields of 60–65% (Scheme I). Selection of the chloroacetyl group to block the phenolic hydroxyl of **4** was a matter of convenience. Conversion of **3** to **2** is best carried out under mild conditions to avoid solvolytic losses of **2**.

Structures of **2** and **3** were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and by high-resolution mass spectroscopy.

Solubility of **2** in water at 25 °C is low, slowing preparation of aqueous solutions of **2** unless the compound is predissolved in a solvent such as ethanol and then added to water. For an ethanolic stock solution containing 10 mg/mL, addition of 3 mL of stock solution to 100 mL of deionized water produces a saturated solution of **2**.

Preliminary taste tests indicate that **2** is approximately 3000 times sweeter than sucrose with full expression of sweetness requiring 2–3 s, as does its analogue **1**. However,

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addition of sodium acetate (1 mg/mL) to dilute solutions of **2** approximately halves the time required for full expression of sweetness. Sweetness lingers briefly, but the tongue's response to other sweeteners taken immediately afterward is altered even after the sweet taste has faded. Standard solutions of sucrose or saccharin seem to increase in sweetness after one or two tastes of **2**, then seem to become less sweet than initially determined as tasting of **2** continues. When tasted as a solid, **2** produces a flavor similar to licorice, but this is not noted when tasted as a dilute solution in water (2–3 mg/100 mL).

Yamato et al. (1977) have prepared and tasted a variety of compounds that are structurally related to **1**. They have indicated that sweetness in **1** and related compounds appears to be linked to the presence of two aromatic centers, one of which must be a 3-hydroxy-4-methoxyphenyl group, linked by an unbranched two-atom bridge. In another correlation of sweetness to structure, DuBois et al. (1977) proposed that **1** and the structurally similar neohesperidose dihydrochalcone achieve equivalent "bent" conformations that meet the requirements of Kier's (1972) "third binding site" model. The isolation of **2** as a racemic mixture in which only the *R* isomer matches the stereochemical features of **1** hinders a similar interpretation. Since racemic **2** seems sweeter than **1** or any of the similar model compounds reported (Yamato et al., 1977), a determination of whether the *S* isomer is sweet or tasteless would be revealing. Attempts to resolve the mixture are in progress.

Even though **2** may be the sweetest compound modeled on phyllodulcin, its application in foods will be limited to dry applications unless it can be stabilized in water. Hydrolysis of **2** in neutral, aqueous solutions is rapid at 100 °C; **2** has a 3-min half-life. Sweetness fades more slowly at 25 °C, disappearing within 7 days. However, the powerful sweetness of **2**, its simple structure and facile synthesis, demonstrates the potential for preparing an acceptable, low-calorie sweetener that mimics structural and conformational features of intensely sweet, natural models.

EXPERIMENTAL SECTION

Proton NMR spectra were measured at 100 MHz on a Varian HA-100 spectrometer and ^{13}C NMR spectra on a Bruker WH-90 with tetramethylsilane (δ 0.0) as the internal standard. Solute concentrations were approximately 20% (w/v). Chemical shifts were measured directly. A Nuclide 1290 DF mass spectrometer was used for high-resolution mass spectroscopy. High-performance liquid chromatography (HPLC) was performed on a Waters Associates ALC/GPC 201, using a 2 mm o.d. × 61 cm column of Corasil I. Operation was isocratic at 0.5 mL/min with 8:1 toluene–diethyl ether.

Melting points were determined in capillary tubes. All chromatographic solvents were proportioned on a v/v basis. Calcium hydride was used to dry collidine and benzene; other solvents and all reagents were used as received when purchased.

3-Chloroacetoxy-4-methoxybenzaldehyde (5). A stirred mixture containing 108 g (710 mmol) of **4**, 500 mL of chloroform, and 125 mL of collidine was kept below 10 °C, treated dropwise with 70 mL (800 mmol) of chloroacetyl chloride over a 1-h period, and then stirred 2 h at 25 °C. The solution was serially extracted with 500-mL portions of water, 0.3 N HCl, and water (2X), chloroform was evaporated and crude **5** recrystallized from diethyl ether (147 g, 91%), mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 9.78 (s, 1, CHO), 6.96–7.74 (complex m, 3, aromatic), 4.28 (s, 2, CH_2Cl), 3.82 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$) δ 189.7 (d, CHO), 165.2 (t, ester CO), 156.1 (m), 140.0 (s), 130.6 (d), 130.2 (m), 123.0 (dd), 112.4 (d), 56.4 (q, OCH_3), 40.5 (t, CH_2Cl); mass spectrum (70 eV, two most intense ions each 14 mass units above *m/e* 34) 39 (10.5), 41 (2.8), 51 (11.1), 53 (11.1), 63 (5.9), 65 (9.7), 77 (5.8), 81 (18.8), 93 (2.4), 95 (2.9), 108 (3.7), 109 (14.5), 123 (12.7), 124 (1.3), 136 (1.0), 137 (5.9), 151 (82.3), 152 (100), 168 (0.4), 179 (0.3), 228 (M^+, 1.7), 230 (M^+, 0.3). Elemental analyses were satisfactory.

2-(3-Chloroacetoxy-4-methoxyphenyl)-1,3-benzodioxan (3). A solution containing 24 g (105 mmol) of **5**, 14.5 g (136 mmol) of trimethyl orthoformate, and 1.5 g (7.9 mmol) of toluenesulfonic acid monohydrate in 300 mL of benzene was stirred and refluxed in a 500-mL round-bottom flask connected to a Soxhlet extractor and protected from moisture. The 33 × 94 mm extraction thimble contained 50 g of Davison molecular sieve 4A (14–30 mesh). Formation of **6** was complete after 1 h, as judged by thin-layer chromatography (TLC) (9:1, benzene–diethyl ether), whereupon the solution was cooled to 40–45 °C, diluted with 200 mL of benzene, and treated with 13 g (105 mmol) of **7**. Reflux through the molecular sieve was resumed for 1.5 h; then the solution was cooled, treated with 2 mL of pyridine, and diluted to 1000 mL with ethyl acetate. The organic layer was extracted with 500-mL portions of dilute aqueous cupric sulfate and water, dried, and evaporated. The crystalline residue was refluxed 2–3 min in 350 mL of methanol, chilled to 0 °C, and filtered to yield **3** (21.95 g, 62%): mp 117–118 °C; $[\alpha]^{25}_{546}$ 0° (*c* 10, chloroform); ^1H NMR ($CDCl_3$) δ 6.85–7.49 (complex m, 7, aromatic), 5.89 (s, 1, acetal CH), 5.02 (q, 2, CH_2), 4.28 (s, 2, CH_2Cl), 3.80 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$) δ 165.2 (t, CO), 153.0 (s), 151.6 (s), 139.3 (s), 130.2 (s), 128.0 (d), 125.5 (d), 124.9 (d), 121.3 (d), 120.8 (s + d), 116.9 (d), 112.3 (d), 98.1 (d, acetal C), 66.6 (t, CH_2O), 56.0 (q, OCH_3), 40.5 (t, CH_2Cl), mass spectrum (70 eV, two most intense ions each 14 mass units above *m/e* 34) 39 (1.8), 41 (0.7), 51 (3.6), 52 (3.5), 65 (1.7), 67 (0.7), 77 (5.7), 78 (15.7), 94 (0.3), 95 (2.5), 106 (9.2), 107 (9.2), 121 (0.9), 123 (1.8), 137 (1.8), 138 (0.3), 151 (16.4), 152 (100), 168 (0.1), 169 (0.2), 183 (3.4), 185 (1.0), 197 (0.2), 199 (0.2), 211 (0.1), 215 (0.1), 227 (3.1), 228 (18.0), 230 (7.5), 231 (0.9), 257 (0.2), 258 (1.4), 259 (0.3), 285 (0.1), 306 (0.8), 308 (0.3), 317 (0.1), 319 (0.1) 334 (M^+, 13.9), 336 (M^+, 4.8); high-resolution mass spectrum 70 eV, calculated for ^{35}Cl ions) theoretical $C_{17}H_{15}ClO_5$: 334.0608, found 334.0606; theoretical $C_{10}H_9ClO_4$ 228.0189, found 228.0190; theoretical $C_8H_8O_3$: 152.0473, found, 152.0469; theoretical $C_8H_7O_3$: 151.0395, found 151.0392.

2-(3-Hydroxy-4-methoxyphenyl)-1,3-benzodioxan (2). A 30-g portion of **3** was dissolved in 300 mL of warm benzene, diluted with 600 mL of methanol containing 70 mmol of barium methoxide, and then stored 18 h at 5 °C. After adding 10 g of ammonium acetate, volatiles were evaporated, and the residue was extracted with two 500-mL portions of chloroform. The chloroform was washed once with 500 mL of water, the water was reextracted with 500 mL of chloroform, and the combined chloroform extracts were washed once with 300 mL of water. Evaporation and crystallization from diethyl ether–*n*-hexane gave **2** (23 g, 95%): mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 6.78–7.19 (complex m, 7, aromatic), 5.86 (s, 1, acetal CH), 5.02 (q, 2, CH_2), 3.84 (s, 3, OCH_3); ^{13}C NMR ($CDCl_3$) δ 153.2 (s), 147.5 (s), 145.7 (s) 130.6 (s), 127.9 (d), 124.8 (d), 121.1 (d), 120.9 (s), 118.3 (d), 116.9 (d), 112.9 (d), 110.5 (d), 98.8 (d, acetal), 66.6 (t, CH_2), 55.9 (q, OCH_3); mass spectrum 70 eV, two most intense ions each 14 mass units above *m/e* 34) 39 (5.1), 41 (1.2), 51 (7.1), 52 (7.8) 63 (2.2), 65 (3.0), 77 (7.7), 78 (17.9), 93 (0.5), 95 (1.6), 107 (69.4), 108 (7.0), 123 (4.4), 124 (1.1), 135 (0.4), 137 (5.3),

151 (47.4), 152 (100), 164 (0.3), 169 (0.4), 184 (0.2), 198 (0.2), 199 (0.3), 212 (0.2), 213 (0.2), 227 (0.4), 229 (0.3), 230 (0.2), 240 (0.4), 257 (0.4), 258 (M^+, 36.3), 259 (M + 1, 5.7); high-resolution mass spectrum (70 eV) calculated for $C_{15}H_{14}O_4$: theoretical 258.0892, found 258.0910; theoretical $C_8H_8O_3$ 152.0473, found 152.0480; theoretical $C_8H_7O_3$ 151.0395, found 151.0392; theoretical C_7H_7O 107.0496, found 107.0503.

Hydrolysis of 2. An ethanolic solution of **2** (50 mg in 2 mL) was added to 100 mL of distilled water held at 100 °C. Samples (25 mL) were withdrawn at 2.5, 5, 7.5, and 10 min, chilled to 25 °C in an ethanol-solid CO_2 bath, and extracted with four 25-mL portions of chloroform. The chloroform was dried, evaporated, and taken up in 1 mL of 8:1 toluene–diethyl ether. Samples were analyzed by HPLC and a 3-min half-life was determined graphically from peak areas of **2** and **4**. Conversion of **7** to an unknown running near the solvent front was detected by TLC (9:1 chloroform–diethyl ether) in the hydrolysis products, approximately 60–70% of **7** being so converted by the end of the experiment.

Sweetness of 2. Reference solutions of sucrose (3, 4, 5, and 6% w/v) were prepared daily, and 2 mg% solutions of **2** (0.2 mL of a 10 mg/mL stock solution of **2** in 99.5% ethanol added to 100 mL of water) were prepared twice daily. All solutions were prepared with deionized water, and held at room temperature (22–24 °C) for 1 h before tasting. At intervals of 4–6 h, each of five persons tasted a single sucrose solution, rinsed his mouth with deionized water, and then tasted the 2 mg % solution of **2**. Retasting of the sucrose solution was not permitted. Sweetness of **2** was then scored as less than, equal to, or greater than the sucrose solution provided. All individuals scored the 2 mg % solution of **2** as isosweet with a 6% sucrose solution. Plans to confirm this result with a trained taste panel and to determine a threshold sweetness level were subsequently suspended, at the recommendation of the ARS Human Studies Review Committee, until approximate LD_{50} values are determined for **2**, **4**, and **7**.

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Gas Chromatographic and Sensory Analysis of Volatiles from Cling Peaches

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The contribution of volatiles to the odor of clingstone peaches was investigated by exit-port sniffing, descriptive flavor analysis, and gas chromatographic (GC) analysis of fresh samples of Halford peaches and of canned samples of Halford plus nine other peach varieties. Volatile constituents were isolated by steam distillation–extraction of the diced, fresh Halfords, and the concentrate was subjected to GC analysis in high-resolution, glass capillary columns. Based on mass spectra and GC retention times, 24 compounds, predominantly esters, monoterpenes, and γ-lactones, were identified. Compounds such as *n*-hexyl acetate, *trans*-2-hexenyl acetate, nonanal, tricosane, and γ-dodecalactone were present in fresh, but not in canned Halfords. Volatiles which varied the most in concentration among the varieties of canned peaches were isoamyl acetate, furfural, linalool, α-terpineol, γ-heptalactone, and geraniol. The γ-lactones, with the exception of γ-decalactone, were present in very small concentrations. Ten judges, trained in descriptive flavor analysis, found large differences among the varieties in: overall peach odor, overall peach flavor, fruity, floral and overcooked notes, and in sweetness and sourness. Equations from stepwise multiple regression indicated the sensory characteristics were dependent on the relative concentrations of the volatile compounds present. Among the ten peach varieties, differences were due more to the relative concentration of esters and monoterpenes than to the γ-lactones. The latter contributed the necessary "peachy" background while the lower-boiling compounds contributed fruity and floral notes.

Studies on the volatiles of peaches have resulted in the identification of approximately 70 compounds. Lactones, particularly γ-lactones, have been implicated in peach aroma by Jennings and Sevenants (1964), Sevenants and Jennings (1966, 1971), Broderick (1966), and Do et al. (1969), based on casual observations, rather than on analytical sensory measurements. To date, most investigations have been focused on freestone, rather than on clingstone peaches, because of the greater aroma intensity of the former. Lim (1963) and Lim and Romani (1964) reported differences in volatile constituents among varieties of freestone peaches, while Do et al. (1969) studied volatiles from freestone peaches differing in maturity. To our knowledge, no attempt has been made to quantitate

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