suming blank determinations. The combined analysis for any one sample may be completed in 25 min. Finally, it is anticipated that this procedure would be applicable to a variety of food products and other biological systems.

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Structure–Taste Relationships among Cyclic Glycols, Levoglucosan, and Methyl Glycopyranosides

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Investigation of the stereochemical requirements for hydroxyl groups in cyclic compounds to elicit a sweet taste showed that, among the diols with known and relatively stable conformations, those that were sweet had oxygen atoms spaced within the range 3.5–5.5 Å. Those that were not sweet had oxygen atoms spaced within the intramolecular hydrogen bonding range (<3 Å) or wider than 5.5 Å. Two synclinal (gauche) vicinal hydroxyl groups in cycloalkanes do not elicit a sweet taste, whereas anticlinal and antiperiplanar conformations of vicinal hydroxyl groups do. In O-heterocyclic glycols and in methyl glycosides, the ring oxygen probably participates with gauche-oriented hydroxyl groups to induce sweetness, because intramolecular hydrogen bonding of an axial hydroxyl group with the ring oxygen reduces sweetness.

The search for nonnutritive sweeteners to replace those of doubtful healthfulness has developed increased interest in establishing a stereochemical basis for sweet taste. Many structural analogues of different classes of sweet compounds have been synthesized to study structure–taste relationships; yet, glycols, the simplest sweet compounds and probably basic for the analysis of sugar sweetness, have not been structurally correlated with taste.

Sugars and sugar derivatives have been correlated by Birch and Lee (1971), Birch et al. (1971), Birch and Lindley (1973), and Dick et al. (1974), peptide analogues by Mazur et al. (1969, 1970), Lapidus and Sweeney (1973), and Van Der Heijden et al. (1978), amino acids, peptides, and proteins by Solms (1969), Lelj et al. (1976), Temussi et al. (1978), and Wieser and Belitz (1977), flavonoid dihydrochalcones by Krbechek et al. (1968) and Horowitz and Gentili (1971), perillartine analogues by Acton et al. (1970) and Unterhalt and Boeschemeyer (1971), phyllodulcin analogues by Yamato et al. (1972, 1977), cyclamate analogues by Unterhalt and Boeschemeyer (1972), and oxathiazinone dioxides by Clauss and Jensen (1973).

Glycols give sweetening powers less than half that of sucrose and obviously do not provide for useful sweeteners. However, the taste of glycols might yield basic information on the primary spacing requirements for electronegative and hydrogen-bonding functional groups in other compounds and in the taste bud receptor site, in view of the molecular theory of Shallenberger and Acree (1967, 1969, 1971) and Shallenberger and Birch (1975). Their theory is distinguished in that it embraces the widest variety of sweet and bitter compounds; moreover, it is sufficiently specific for experimental verification.

The primary objective of this investigation was to determine the spacing requirements for hydroxyl oxygen atoms in glycols of relatively fixed conformations to elicit a sweet taste. Glycols of known or predictable conformations were selected from the cycloalkanediols, anhydro and dianhydro alditols, and a group of methyl 4,6-*O*-methylene-D-glycopyranosides containing only two free hydroxyl groups. Levoglucosan, anhydro alditols, and methyl glycosides also were selected for comparative purposes. Their sweet and bitter tastes were evaluated for intensity by a trained taste panel under controlled environmental conditions.

EXPERIMENTAL SECTION

Cyclic Groups. These compounds were synthesized by published methods or purchased. They were recrystallized, sublimed, or distilled to the established melting or boiling points, and known derivatives were prepared to confirm their identity (Table I). Each compound presented to the taste panel gave only one large symmetrical peak by gas–liquid chromatography (GLC) of the trimethylsilyl (Me_3Si) ether derivatives. The *cis*- and *trans*-1,2- and 1,3-cyclohexanediols were separated by the GLC conditions adopted, but the *cis*- and *trans*-1,4-cyclohexanediols were not (Table I). Identity of the glycols also was confirmed through identity of their infrared absorption bands in carbon tetrachloride (OH stretching) with those published by Kuhn (1952, 1954) and Brimacombe et al. (1958).

Anhydro Sugars and Alditols. These compounds were prepared by well-known methods. The purity was established by GLC. Single, symmetrical peaks were ob-

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Table I. Authentication of Compounds Prepared for Taste Panel

compound	compound mp, °C found	compound mp, °C reported	derivative mp[a] found	derivative mp[a] reported	GLC of Me_3Si ethers RT, min	GLC of Me_3Si ethers temp, °C	preparative method (or source)
cis-1,2-cyclopentanediol			89-90	92 T	14.5	69	Brutcher and Evans (1958)
trans-1,2-cyclopentanediol			108-109	109 T	13	60	Roebuck and Adkins (1955)
cis-1,2-cyclohexanediol	96-97.5	98			14.5	75	Wilson and Read (1935)
trans-1,2-cyclohexanediol	103-104	104			19	75	Aldrich, recrystd
1-methyl-*trans*-3,4-cyclohexanediol	66-68	68			18	65	Adkins and Roebuck (1948)
cis-1,3-cyclohexanediol	85-86	85.5	109-100	108 T	20	75	Dale (1961)
trans-1,3-cyclohexanediol	118-119	118-120	88-98	90 T	14	75	Dale (1961)
cis-1,4-cyclohexanediol	112-113	112.4	98-99	98-99 T	21.5	75	Sugihara and Bowman (1958)
trans-1,4-cyclohexanediol	141-142	143	138-139	159 T	21.5	75	Owen and Robins (1949)
trans-1,2-cycloheptanediol	63-65	64-65			24.5	75	Aldrich
1,4:3,6-dianhydro-D-mannitol	83-84.5	87-88		133 B	13	100	Foster and Overend (1951)
1,4:3,6-dianhydro-D-glucitol	63-64	61-63		102-103 B	12	100	Atlas, recrystd
1,4-anhydroerythritol			174-175	173-174 NB	11.5	75	Otey and Mehltretter (1961)
1,6-anhydro-β-D-glucopyranose	180-181	180-181	110	109-110 A	12.5	130	Wolff et al. (1968)

[a] A = triacetate; B = dibenzoate; NB = bis(*p*-nitrobenzoate); T = bis(*p*-tolysulfonyl ester).

tained, and known derivatives were prepared to confirm their identity.

Methyl Glycosides. These sugar derivatives were prepared by well-known methods or were purchased in the purest available form. Anomeric purity was established by GLC under conditions that separated the α and β anomers. Single, symmetrical peaks were obtained. The methyl 4,6-*O*-methylene-D-glycopyranosides were prepared as described by Goodwin and Hodge (1973).

Gas–Liquid Chromatography. An F and M Model 700 laboratory chromatograph with flame ionization detector was fitted with a $^1/_8$ in. × 6 ft tubular stainless steel column containing 3% JXR silicone gum on 100–120-mesh Gas-Chrom Q support (Anspec, Ann Arbor, Mi). Trimethylsilyl ether derivatives (Sweeley et al., 1963) of each polyhydric compound were prepared and chromatographed at the appropriate temperature (Table I). Methyl pentopyranosides were analyzed at 110 °C and hexopyranosides at 130 °C, with temperature rise of 1 °C/min. Other conditions were as follows: injection port temperature, 200 °C; detector temperature, 230 °C; helium pressure, 50 lb/in.^{2}; rotometer setting, 2.

Infrared Measurements. The spectra of each cyclic diol were recorded by a Perkin-Elmer Model 612 spectrometer containing 0.005 M solutions of the sample in carbon tetrachloride. Hydroxyl stretching frequencies were examined critically for free and intramolecularly bound hydroxyl groups according to the doctrines of Kuhn (1952, 1954).

Conductivity Measurements. Conductivities of 0.5 M boric acid solutions of the diols (0.1 M) were measured with a Type CDM2e meter (Radiometer A/S, Copenhagen) at 70 Hz, 25 °C. Differences in conductivity between the boric acid solution with and without solute were calculated according to Boeseken (1949) to determine the coplanarity of hydroxyl groups.

Taste Panel Evaluations. Eight persons were selected for their ability to detect the sweet taste of a 0.5% solution of sucrose in water and to evaluate consistently both the sweet and bitter tastes of methyl β-D-glucopyranoside at 3% concentration in water. Six of the panel members were already experts at evaluating bitter taste in soybean products.

Panel sittings were conducted in private booths under controlled lighting, relative humidity (50%), and temperature (25 °C). Samples were submitted as aqueous solutions (7 mL) in glass beakers. Tasters were instructed to taste first with the tip of the tongue for sweetness and then to roll the solution to the back of the tongue to evaluate bitterness. Time for sweetness to appear and duration of sweetness were estimated. Other sensations recorded, but not evaluated, were menthol-like cooling, medicinal flavors, and astringency. Compounds were tasted at 3.00, 4.00, or 5.00 (w/w) concentration in charcoal-filtered tap water. Reference solutions of 0.5, 1.0, 1.5, and 2.0% (w/w) sucrose in the same water were given to each taster. Ratings in tenths between the concentrations of the reference sucrose solutions were encouraged. No more than four compounds were evaluated at one sitting of the panel.

Bitterness was evaluated on a scale of 0, 1, 2, and 3, wherein 2 was judged to be equivalent in bitterness to a reference 0.05% caffeine solution. A rating of 3 designated all degrees of bitterness stronger than the reference caffeine solution.

Relative sweetness to sucrose (=1.00) was calculated by dividing the equivalent sucrose rating by the concentration of the test solution. The average deviation from the average was calculated from the sweetness and bitterness ratings for each compound at each sitting of the panel. Occasional aberrant ratings that varied more than 3 times the average deviation were omitted from the final calculations.

RESULTS AND DISCUSSION

Cyclic Glycols and Dihydric Phenols. Simple aliphatic diols, e.g., ethylene glycol, trimethylene glycol, and 1,4-butanediol, are sweet in varying degrees; but, because of the flexibility of their linear chains, they do not provide acceptable models for studying the spacing requirements for hydroxyl groups to elicit a sweet taste. We selected cyclic and bicyclic diols to provide compounds with known and relatively stable conformations. By means of structural (Dreiding) models of these conformations, spacings of the oxygen atoms of hydroxyl groups were measured. Many previous investigations have provided knowledge of the most stable conformations of the compounds that we selected and particularly those of Kuhn (1952, 1954), Cole and Jefferies (1956), Brimacombe et al. (1958), and Dale (1961).

Conformational formulas of the selected cyclic diols and levoglucosan (1,6-anhydro-β-D-glucopyranose) are shown in Figure 1. Code letters following each numeral indicate qualitatively the sweetness of each compound. Quantitative sweetness and bitterness evaluations are listed in Table II. Because panel members could consistently

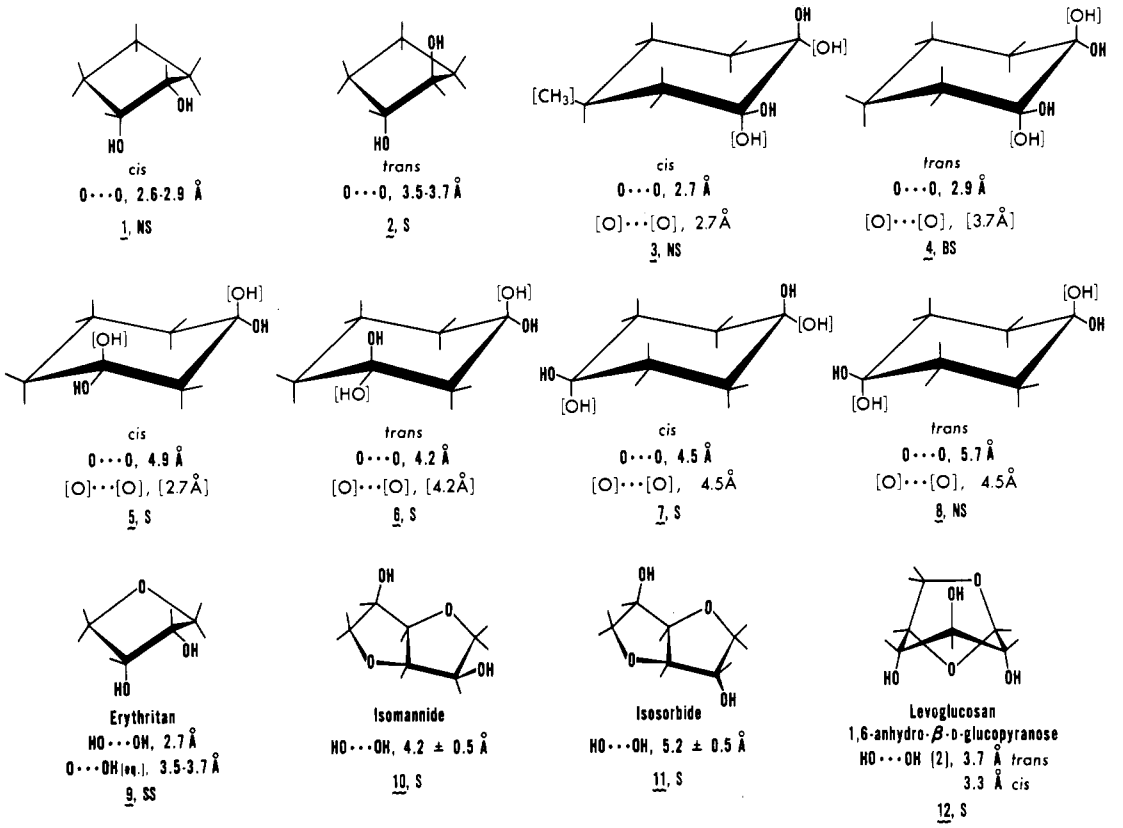


Figure 1. Conformation structures of cyclic diols and levoglucosan. S = sweet; SS = slightly sweet; BS = borderline sweet; NS = not sweet.

Table II. Taste Panel Ratings of Cyclic Diols, Levoglucosan, and D-Glucose

formula no. (Figure 1)	compound	concn in water, % by wt	no. of tasters	sweetness, panel score (equivalent sucrose concn)	bitterness (0.05% caffeine solution = 2)
1	*cis*-1,2-cyclopentanediol	3	4	0.2 ± 0.2	3
		4	5	0.1 ± 0.1	3
2	*trans*-1,2-cyclopentanediol	3	4	1.3 ± 0.4	3
		4	5	1.2 ± 0.9	3
3	*cis*-1,2-cyclohexanediol	4	11	0.1 ± 0.2	2.5
4	*trans*-1,2-cyclohexanediol	4	11	0.6 ± 0.3	3
5	*cis*-1,3-cyclohexanediol	4	6	1.3 ± 0.3	2
6	*trans*-1,3-cyclohexanediol	4	6	1.3 ± 0.4	2.5
7	*cis*-1,4-cyclohexanediol	4	3	1.2 ± 0.2	3
8	*trans*-1,4-cyclohexanediol	4	11	0.2 ± 0.2	2.5
	1-methyl-*trans*-3,4-cyclohexanediol	4	6	0.0 ± 0.0	3
	trans-1,2-cycloheptanediol	4	4	0.1 ± 0.1	3
9	*cis*-1,4-anhydroerythritol	5	7	0.8 ± 0.3	2.5
10	1,4:3,6-dianhydro-D-mannitol	5	6	1.3 ± 0.2	1.5
	(isomannide) *cis*-2,4-diol	3	7	1.0 ± 0.3	2
11	1,4:3,6-dianhydro-D-glucitol	5	7	1.2 ± 0.3	2
	(isosorbide) *trans*-2,4-diol	3	7	1.0 ± 0.1	
12	1,6-anhydro-β-D-glucopyranose	4	6	1.8 ± 0.3	1.5
	(levoglucosan) *trans*-2,3,*trans*-3,4-triol	3	8	1.2 ± 0.2	1.5
		2	6	0.85 ± 0.3	1.3
		1	6	0.42 ± 0.3	0.5
	D-glucose, equilibrated	3	6	1.3 ± 0.4	0.2
		2	6	0.9 ± 0.3	0.0

detect the sweet taste of 0.5% sucrose solutions, equivalent sucrose concentration ratings of 0.5 or higher indicates a sweet compound. In addition to the panel-evaluated compounds listed in Table II, 1-methyl-*cis*-3,4-cyclohexanediol was found to be bitter and not sweet by three panel members. Moreover, Kingsbury (1970a,b) could detect only bitterness in the three cis and trans 3-methyl-1,2-cyclohexanediols that he reported.

The diols are grouped according to their relative sweetness to sucrose in Table III. The interoxygen spacings are estimated to 0.1 Å from Dreiding models and knowledge of the most stable conformations. The spacings shown in parentheses in Table III and Figure 1 are those of possible alternate conformations. For the nonsweet diols with interoxygen spacings of less than 3 Å, intramolecular hydrogen bonding was indicated by the infrared spectra of carbon tetrachloride solutions. The hydroxyl groups of the sweet diols are not spaced closely enough to permit intramolecular hydrogen bonding. Although the conformer of *cis*-1,3-cyclohexanediol (5, Figure 1, in parentheses) does

Table III. Correlation of the Relative Sweetness of Diols with Their Interoxygen Spacings and Intramolecular Hydrogen Bonding

compound	relative sweetness, sucrose = 1	O···O spacing (HO···OH), Å	intramolecular H bonding in CCl_4 by IR
sweet diols			
trans-1,2-cyclopentanediol	0.36	3.5–3.7	0
cis-1,3-cyclohexanediol	0.33	4.9 (2.6)	0 (+)
trans-1,3-cyclohexanediol	0.33	4.2 constant	0
cis-1,4-cyclohexanediol	0.30	4.5	0
cis-2,5-diol of isomannide	0.32	4.2 ± 0.5	0 (+)[a]
trans-2,5-diol of isosorbide	0.28	5.2 ± 0.5	0 (+)[a]
trans- and *cis*-diols of levoglucosan	0.43 ± 0.02	3.7 (3.3)[b]	0 (+)[a]
1,3-dihydroxybenzene	sweet	4.8	0
1,3,5-trihydroxybenzene			
borderline sweet			
1,4-dihydroxybenzene	weak	5.5	0
trans-1,2-cyclohexanediol	0.15	2.9 (3.7)	+ (0)
1,4-anhydroerythritol	0.16	2.6–2.9 (3.7)[c]	+ (0)[a]
nonsweet diols			
cis-1,2-cyclopentanediol	0.06	2.6–2.9	+
cis-1,2-cyclohexanediol	0.03	2.7[d]	+
trans-1,2-cycloheptanediol	0.03	2.7[d]	+
1-methyl-*trans*-3,4-cyclohexanediol	0.0	2.9	+
1,2-dihydroxybenzene	none	2.7	+
trans-1,4-cyclohexanediol	0.05	5.7	0

[a] For OH to ring oxygens. [b] 3.3 Å between C(2)-OH and C(4)-OH in the crystalline structure by X-ray analysis. [c] 3.7 Å between OH and ring oxygen in a twist conformation. [d] By infrared analysis (Kuhn, 1954).

show such bonding in carbon tetrachloride, it is the diequatorial form that is most stable in aqueous solutions (Dale, 1961).

Table III shows that all of the sweet diols and dihydric phenols have interoxygen spacings within the range 3.5–5.5 Å. The distances between oxygen atoms for the nonsweet aromatic polyols do not fit into the 3.5–5.5-Å range; however, aromatic polyols should not be correlated with cyclohexanediols, because complications are introduced by differences in binding sites (π-electron cloud and the rigid planar benzene ring).

The dihydric phenols and their mono-*O*-methyl ether derivatives (Figure 2) were not submitted to the taste panel because they produce a burning, desensitizing effect on the tongue that interferes with subsequent tasting. Informal tasting, which confirmed the taste evaluations of Hlasiwetz and Habermann (1875), showed that the dihydric phenols follow the same spacing requirements for sweetness as was determined with the alicyclic diols. Hydroquinone, with oxygen atoms spaced at the outer limit of 5.5 Å, is only weakly and fleetingly sweet. Two cyclic diols with oxygen atoms spaced wider than 5.5 Å were not sweet, viz., *trans*-1,4-cyclohexanediol and 1,2,3,4-tetrahydro-1,5-naphthalenediol.

In harshly sweet resorcinol, or in weakly sweet hydroquinone (but not in strongly sweet phloroglucinol with three hydroxyl groups), blocking of one of the hydroxyl groups with a methyl ether group effectively blocks the sweetness (Figure 2). Furthermore, ethylene glycol (maximum O···O spacing, 3.7 Å) is obviously sweet, whereas 2-methoxyethanol is not. It is apparent from our data that oxygen atoms of a methoxy group in the diol group of compounds does not serve as B in the AH,B system of Shallenberger and Acree (1969) to induce a sweet taste.

The *trans*-1,2-cyclopentanediol (2), first stated to be sweet by Meiser (1899), was proved to be sweet by our panel. However, two members of the panel at two different sessions failed to taste the sweetness that was obvious to other members of the panel, probably because strong bitterness was also perceived. This disparity illustrates the difficulty of evaluating sweetness in the presence of

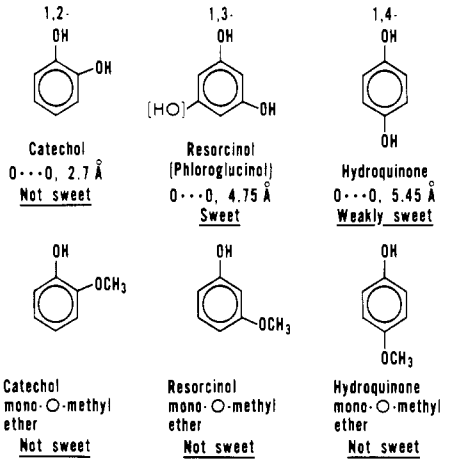


Figure 2. Structures and taste evaluations of dihydric phenols and their *O*-methyl ethers.

strong bitterness. Although all of the cyclic diols were judged to be as bitter or more bitter than 0.05% caffeine solution, we believe that this problem was overcome by our trained taste panel. Similar disparities were seldom encountered with the other diols.

The *trans*-1,2-cyclohexanediol (4) gave a borderline degree of sweetness, whereas the cis isomer (3) was not sweet. For the trans isomer, the diequatorial configuration of hydroxyl groups is the most stable; nevertheless, a small amount of the diaxial conformer (shown in parentheses) should be present in the aqueous solution. In the diaxial conformer, the interoxygen spacing is 3.7 Å, which is within the specified range for sweetness. The interoxygen spacing of the cis isomer does not exceed 3 Å in any of its possible conformations. When a *C*-methyl group is added to the cyclohexane ring, as in 1-methyl-*trans*-3,4-cyclohexanediol, the all-equatorial conformation (O···O), 2.9 Å would be more stable, and this compound was not at all sweet. It is quite possible, however, that the mere addition of a methyl group to the ring could have rendered the molecule inactive.

trans-1,2-Cycloheptanediol is not sweet. It is strongly

Table IV. Sweetness and Bitterness of Methyl Glycopyranosides[a]

with no intramolecular H bonding by an axial OH				with axial C(2)- or C(4)-OH bonding to ring O			
compound	no. of tasters	rel sweetness[b]	comparative bitterness[c]	compound	no. of tasters	rel sweetness[b]	comparative bitterness[c]
			Hexopyranosides (Four Free OH Groups)				
α-D-allo	6	0.53	1	α-D-altro	6	0.33	<1
α-D-gluco	18	0.52	<1	α-D-galacto[d]	19	0.30	1
β-D-gluco	18	0.33	3	β-D-galacto	19	0.37	1
			Pentopyranosides (Three Free OH Groups)				
α-D-xylo	8	0.48	1	β-L-arabino	13	0.20	2
β-D-xylo	8	0.40	1	α-D-lyxo	13	0.27	2
			4,6-*O*-Methylenehexopyranosides (Two Free OH Groups)				
α-D-galacto	6	0.33	2	α-D-altro	6	0.17	3
α-D-gluco	6	0.27	3	α-D-manno	6	0.23	3
	overall av:	0.41			overall av:	0.28	

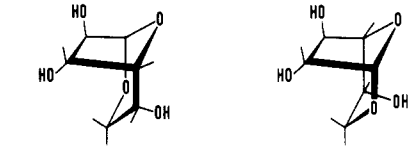
[a] Tasted at 3.00% (w/w) concentration in charcoal-filtered tap water. [b] Sucrose = 1.00; overall average deviation from the average: ±0.07. [c] Vs. 0.05% caffeine solution = 2; overall average deviation from the average: ±0.5. [d] Weighed as the monohydrate, 8.5% H_2O.

bitter. These hydroxyl groups tend to occupy a synclinal or gauche configuration in carbon tetrachloride solution in which the oxygen atoms are spaced less than 3 Å apart; furthermore, intramolecular hydrogen bonding is evident from the infrared spectrum (Kuhn, 1954).

Significantly, *trans*-1,3-cyclohexanediol (**6**) is sweet. Unlike the *cis*-1,3- and *cis*-1,4-cyclohexanediols (**5** and **7**), this compound cannot give spacings narrower than 4.2 Å in any of the less-favored conformations. We could obtain no evidence from infrared or conductivity measurements that **7** adopts a boat form with a close spacing of the hydroxyl groups. No intramolecular hydrogen bonding was detected.

If the diols approach the receptor site on the tongue as the AH,B system of Shallenberger and Acree (1969, 1971), then it can be expected that the corresponding B,AH site of the receptor also presents a spacing between 3.5 and 5.5 Å.

Anhydro Sugars. Levoglucosan (1,6-anhydro-β-D-glucopyranose-*1-C*), a bicyclic triol of relatively fixed conformation (**12**), was not considered to be sweet by Shallenberger and Acree (1969); however, a bittersweet taste was reported by Shallenberger and Birch (1975). This compound was cited by Shallenberger and Acree to hypothesize that an antiperiplanar configuration of vicinal hydroxyl groups does not induce sweetness, whereas synclinal (gauche) configurations of vicinal hydroxyl groups do. As Table II shows, our taste panel found levoglucosan to be as sweet as equilibrated D-glucose solution at 2% and at 3% concentrations, despite the higher degree of bitterness in the levoglucosan solutions. Considering first that the six-membered ring is in the chair form (**12**, Figure 1), both O···O spacings of the anticlinal hydroxyl groups are close to 3.7 Å. The cis C(2)–OH and C(4)–OH oxygen atoms are separated by 3.3 Å, outside the range for intramolecular hydrogen bonding. A strong intramolecular hydrogen bond can form between the C(3)–OH and the nearer heterocyclic oxygen atom in the five-membered ring (O··· about 2.7 Å), but this spacing should not induce a sweet taste in view of the analysis shown in Table III. Table III also shows that intramolecular hydrogen bonding was actually detected in the infrared spectrum. Should the six-membered ring adopt a boat conformation in aqueous solution, all O···O spacings, including those to the ring oxygen atoms, would lie between 3.2 and 4.8 Å and strong intramolecular hydrogen bonding would not occur. The boat conformation was not detected by X-ray analysis of crystalline levoglucosan; however, it could exist in aqueous solutions, considering the hydrogen bonding of water to equatorial gauche hydroxyl groups that occurs with D-glucose in water.



D(+)-glucosan
1,6-anhydro-β-D-glucofuranose
HO···OH, 3.6, 4.0, 5.5 Å
13, S

D(+)-galactosan(1,4-α-1,6)
14, S

Figure 3. Conformational structures of 1,6-anhydro-β-D-glucofuranose and 1,6-anhydro-α-D-galactofuranose.

Two other anhydro sugars were tasted informally, because only small amounts were available, viz., 1,6-anhydro-β-D-glucofuranose and 1,6-anhydro-α-D-galactofuranose (Figure 3, **13** and **14**). Both compounds were distinctly sweet. They contain trans-oriented hydroxyl groups in the tetrahydrofuran ring and one additional hydroxyl group. The interoxygen spacings of 3.6, 4.0, and 5.5 Å would be conducive to sweet taste. In cyclic polyhydroxylic molecules, only two properly spaced hydroxyl groups induce a weak sweetness in the presence of strong bitterness; one or more additional hydroxyl groups, properly spaced, increase the sweetness and reduce the bitterness.

O-Heterocyclics and Methyl Glycosides. Erythritan (1,4-anhydroerythritol, **9**) and *cis*-1,2-cyclopentanediol (**1**) are the only compounds listed that gave a strong conductivity in aqueous boric acid solution. The hydroxyl groups are therefore cis and closely spaced (Boeseken, 1949). Whereas *cis*-1,2-cyclopentanediol is not sweet, erythritan does show a borderline degree of sweetness (Table II). For determination of whether the heterocyclic oxygen atom is interacting (as B in the AH,B system of Shallenberger and Acree), a group of methyl 4,6-*O*-methylene-D-hexopyranosides were synthesized (Goodwin and Hodge, 1973) (Figure 4). The α-D-gluco (**17**), α-D-galacto (**18**), and α-D-manno (**19**) derivatives contain vicinal synclinal (gauche) hydroxyl groups. These do not induce sweetness in the cyclohexanediols. Yet, these *O*-methylene derivatives gave detectable sweetness in the presence of strong bitterness (Table IV). More model compounds need to be synthesized and tasted, but now it appears that the pyranose ring oxygen (and the heterocyclic oxygen of erythritan) can participate with hydroxyl groups across the ring (spaced at 3.7 and 4.0 Å) to induce sweetness.

Table IV shows a structure–taste correlation that is

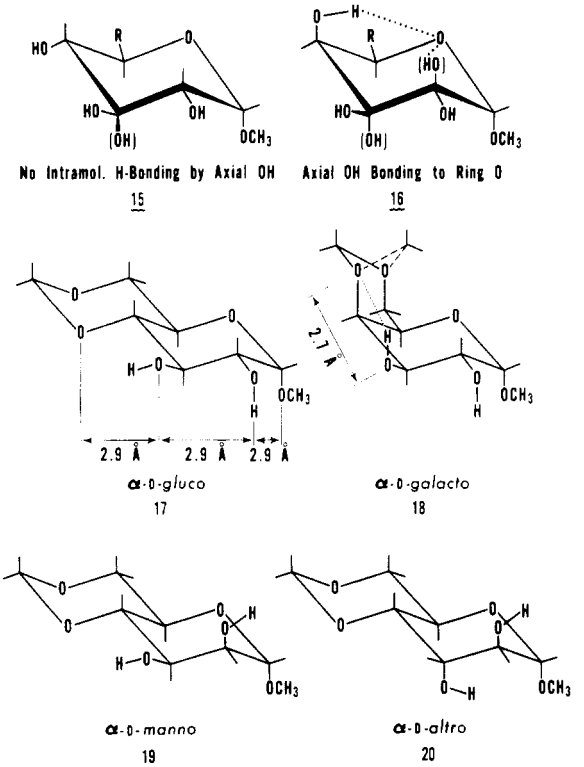


Figure 4. Conformational structures of methyl glycosides and 4,6-*O*-methylene-D-glucopyranosides.

important for evaluating the molecular theory of Shallenberger and Acree. In this divided table, the methyl glycosides (and derivatives) on the left (**15**, Figure 4) do not contain an axial hydroxyl group capable of forming an intramolecular hydrogen bond with the pyranose ring oxygen. Those on the right (**16**, Figure 4) do have this capability. As the sweetness evaluations show, the left-hand group is significantly sweeter than the right-hand group. Shallenberger (1963) has cited the inhibiting effect of intramolecular hydrogen-bonding axial hydroxyl groups in producing the lower sweetness of D-galactose and D-mannose relative to that of D-glucose. This effect is present also in the α-D-altrosides, β-L-arabinoside, and α-D-lyxoside. It was attributed to an inactivation of the hydroxyl group that is involved in the intramolecular hydrogen bonding, but it could also involve an inactivation, through lowering of the basicity or availability of a participating ring oxygen atom.

A rather well-known factor affecting sugar and polyalcohol sweetness is apparent in Table IV. As the number of hydroxyl groups on the sugar ring increases, sweetness increases. This effect is obvious also in the tasting of resorcinol and phloroglucinol. Phloroglucinol (Figure 2, parentheses), with three evenly spaced hydroxyl groups, is lastingly sweet and much more pleasant to taste than the harshly sweet resorcinol with only two hydroxyl groups. Table II shows that levoglucosan, with three hydroxyl groups, is sweeter and less bitter than the sweet glycols. The mildly sweet and bitter glycols therefore lack a third important function (hydroxyl group or electronegative atom) in their molecules that is necessary for a sugar-like sweetness.

As a result of this investigation, we propose the following: (1) For sweet taste induction from two hydroxyl groups in a relatively fixed conformation, the interoxygen spacing should reach beyond the intramolecular hydrogen-bonding distance and fall within the range 3.5–5.5 Å. (2) The presence of two gauche-oriented hydroxyl groups alone in a cyclic molecule does not induce a sweet taste; however, in the presence of a third electron negative functional group, properly spaced, they may do so. We recognize that molecular parameters other than the interatomic spacings of functional groups are involved in the induction of sweet taste. Only the spacings, a prime consideration in the theory of Shallenberger and Acree, were investigated here.

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Sweetness and Bitterness of Some Aliphatic α,ω-Glycol D-Glucopyranosides

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Mono- and di-*O*-β-D-glucopyranosides containing a hydrophobic aglycon consisting of aliphatic α,ω-glycols of the 3C, 4C, 6C, and 8C series were prepared and tasted. 2-Hydroxyethyl mono-*O*-α- and -β-D-glucopyranodies and allyl mono-*O*-α-D-glucoside were definitely sweet; however, 2-hydroxyethyl mono-*O*-β-D- and allyl mono-*O*-α-D-glucosides gave a bitter aftertaste. The hydroxyalkyl mono-*O*-β-D-glucosides with extended alkylene chains and allyl mono-*O*-β-D-glucopyranoside were bitter with no sweetness. The crystalline di-*O*-β-D-glucosides with extended alkylene chains (4C, 6C, and 8C) and the noncrystalline 3-hydroxypropyl mono-*O*-β-D-glucoside were water soluble but tasteless. 1,4-Anhydroerythrityl mono-*O*-β-D-glucoside was bitter and not sweet.

The search for stereochemical and structural requirements for a compound to elicit an intensely sweet taste has produced recognition of the importance of a hydrophobic or lipophilic site in the sweet molecule in addition to specifically oriented hydrophilic sites (Deutsch and Hansch, 1966; Kier, 1972). The binary hydrogen-bonding theory of sweet taste induction (Shallenberger and Acree, 1969, 1971) has been extended to include a third hydrophobic bonding area spaced away from the hydrogen-bonding sites (Shallenberger and Birch, 1975; Shallenberger and Lindley, 1977; Van Der Heijden et al., 1978; Shallenberger, 1980). Hodge and Inglett (1974) correlated the structures of five intensely sweet glycosides of botanical origin and pointed to a widely extended hydrophobic area between polar hydrophilic end groups that was common to all five sweet glycosides. Whether the dispersed hydrophobic area requires dimensional and spatial specificity needs to be examined more fully.

The objective of this investigation was to synthesize mono- and diglucosides of a series of alkanediols which contain hydrophilic–hydrophobic–hydrophilic arrangements of the functional groups for structure–taste correlations. Several new diol glucosides were prepared for this purpose.

EXPERIMENTAL SECTION

Preparative reactions were monitored by thin-layer chromatography (TLC). Purity of the compounds was established by TLC, gas–liquid chromatography (GLC), melting point (mp), and elemental analyses. TLC was conducted on 0.25-mm layers of EM Reagent silica gel G (Brinkmann Instruments, Inc.) with air-dried plates. The spots were detected by spraying with 5% ethanolic sulfuric acid and charring. TLC was performed with 50% ethyl acetate–benzene (v/v) for acetylated compounds and 23:10:2 methyl ethyl ketone–water–absolute ethanol (v/v) for deacetylated compounds. The acetylated glucosides were isolated by dry column chromatography on silica gel G (type 60, EM Reagents, EM Laboratories, Inc., Elmsford, NY) (5% water), using a 2.5 × 85 cm column, with 50% ethyl acetate–benzene and 70% ethyl acetate–hexane (v/v) as the eluant. Deacetylation was performed with sodium methoxide in dry methanol solutions (Thompson and Wolfrom, 1963), and the solution was deionized by stirring with methanol-washed Amberlite IR-120 (H^+) ion-exchange resin (Rohm and Haas Co., Philadelphia, PA.). GLC analyses of trimethylsilyl ethers (Sweeley et al., 1963) of the glucosides were recorded on an F and M Model 700 laboratory chromatograph with a flame-ionization detector, which was fitted with a $^1/_8$ in. × 6 ft stainless steel column containing 3% JXR silicone gum on 100–120-mesh Gas-Chrom Q support (Anspec, Ann Arbor, MI). Single symmetrical peaks were obtained. ^1H NMR spectra were recorded with a Varian Model HA-100 spectrometer: resonances were identified by spin-decoupling experiments and chemical shifts are referred to internal tetramethylsilane. Products were vacuum-dried in the presence of phosphorus pentaoxide for 24–48 h at room temperature before analyses. Melting points, measured in capillary tubes, are not corrected.

Mono- and Di-*O*-β-D-glucopyranosides (**4**, **6**, **8**, **13**, **15**, **17**, and **19**) were prepared by a modification of the procedure of Schroeder et al. (1974). Modification involved a prolonged reaction time (18 h at 25 °C) in purified 1,4-dioxane (Wiberg, 1960) containing Drierite (W. A. Hammond Drierite Co., Xenia, OH). Mono- and di-*O*-tetra-*O*-acetyl-β-D-glucopyranosides (**3**, **5**, **7**, **12**, **14**, **16**, and **18**) were

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