Structure-Taste Relationships in Oximes Related to Perillartine

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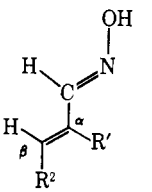
High taste intensity and varying but significant degrees of sweetness were found in a number of oximes analogous to perillartine. These oximes share with perillartine several specific structural features: the aldoxime functional group; *syn*-isomerism of the oxime; olefinic unsaturation conjugated with the oxime; substitution on the α-carbon; and *trans* disposition of the double bond with respect to the oxime and the β-substituent. The exclusively *syn* isomerism of these oximes was observed to be consequent to the presence of the conjugated double bond bearing an α-alkyl substituent. Replacement of the oxime as functional group in this system greatly diminished taste intensity and completely abolished sweetness. Saturation of the conjugated olefinic bond also abolished sweetness, but permitted high taste intensity to be retained.

Interest in the flavor of organic compounds has existed since the early days of organic chemistry. Despite this, there have been few systematic studies on the relationship between chemical structure and flavor published in the literature. Existing generalizations and correlations are largely based on scattered, qualitative taste data, much of it from the classical era of organic chemistry (Cohn, 1914; Ferguson and Lawrence, 1958; Kulka, 1967; Moncrieff, 1967). Methods for reproducible, quantitative evaluation of flavor have been developed in recent years, but these methods have rarely been coordinated with chemical synthesis in a structure-function study (Hamor, 1961; Inglett *et al.*, 1969; Kubota and Kubo, 1969; Mazur *et al.*, 1969). Compounds with a variety of structures, apparently unrelated, have shown sweetness, and it has been difficult to accommodate them within a unified theory. It seems advisable to study carefully defined structural changes within a given class of compounds. The present study has adopted the perillartine molecule (**1**), the oxime of perilla aldehyde, as starting point in a systematic study of structure-flavor relationships.

Examinations of the literature revealed that a number of aldoximes, as isolated examples, possess a sweet taste. Perillartine (Acton *et al.*, 1970; Furukawa and Tomizawa, 1920) apparently is the only one with commercial application, and is made and used in Japan as a sweetener for tobacco (Tsuzuki and Yamashita, 1968). As a terpene derivative, it belongs to a class of compounds where pleasing responses to odor stimuli are commonly found. It was regarded as significant that the oxime function can be included among the AH-B systems suggested by Shallenberger and Acree (1967) as responsible for sweetness. There was an implication that sweetness of oximes might be related to *syn-anti* isomerism, in reports that for three isomeric pairs of oximes (of perilla aldehyde, *p*-anisaldehyde, and 5-benzylfurfural), one isomer in each case was sweet and the other tasteless (Moncrieff, 1967). We have recently shown that perillartine is the *syn*-oxime and that the so-called tasteless isomer of perillartine is in reality the HCl adduct (**2**) (Acton *et al.*, 1970). It seemed important also to reexamine the oximes of *p*-anisaldehyde and 5-benzylfurfural (Gilman and Dickey, 1930), especially because of confusion in the isomeric identity of oximes in older literature.

METHOD OF APPROACH

In planning systematic structural variation of the perillartine molecule, it was assumed that the oxime was the functional group chiefly associated with taste, and that the isopropenylcyclohexene system was the carrier group. Consequently, all but one (**6**) of the compounds studied have been oximes. The carrier group, of course, can either enhance or mask the taste effect of the functional group. The compounds (Figure 1; Table I) can be classified according to the nature of the carrier group: those which retain the isopropenylcyclohexene skeleton, simple alicyclic derivatives, open chain analogs, and aromatic aldoximes. Most of the oximes have three structural features in common, as shown in (**a**): conjugated olefinic



(a)

unsaturation; alkyl substitution (sometimes as part of a ring) on the α-carbon; and *trans* geometry of the olefinic bond (*i.e.*, *trans* orientation of the oxime *vs.* the β-substituent). It is apparently in consequence of these features that these oximes are formed entirely as the *syn* isomers, with no observed tendency to isomerize to *anti* oximes. We have recently suggested that "α,β-unsaturated aldoximes bearing an alkyl substituent on the α-carbon exist only in the *syn* form" (Acton *et al.*, 1970). The convenience in preparation and handling of this class of oximes is a practical advantage. Unlike most oximes, these can be stored in solution, or exposed to variation in pH, without risk of isomerization. It has been stated (Wolkowski *et al.*, 1970) that the *s-trans* conformation is favored, and the structures in Figure 1 are drawn accordingly. α,β-Unsaturated aldehydes without an α-alkyl substituent (*trans*-2-hexenal, *trans*-2-heptenal, *trans*-2-octenal, *trans*-2-dodecenal) formed mixtures of both *syn* and *anti* oximes, as oils, contaminated by isoxazole formation; the separation and evaluation of these oximes has not been pursued. Troskiewicz and Suwinski (1966) reported that α,β-unsaturated, α,β-disubstituted ketoximes exist in only a single form (with the OH *anti* to the olefin). Here, too, substitution on the olefinic α-carbon was critical, since β,β-disubstitution permitted mixtures of ketoximes to be formed. Somewhat surprisingly, it has been predicted (Leibovici, 1968) and reported that acrolein oxime, the aldoxime lacking either α- or β-substitution, exists only in the *syn* form [(Wolkowski *et al.*, 1970); the terms *anti* and *syn* as defined in this paper correspond to *syn* and *anti*, respectively, in common usage].

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Table I. Taste Evaluation of Compounds

Compound Number	Relative Taste Intensity: Solid[a] (direct comparison)	Relative Taste Intensity: Solution[b] (molar comparison)	Solution of Unit Intensity[c] (molar conc.)	Observed Tastes: Sweet (Percent of Total)	Observed Tastes: Bitter (Percent of Total)	Observed Tastes: Other
4-Isopropyl-1-cyclohexene Analogs						
1	2.5	3100	0.00016	71 74	18 7	sour > gingery > mint
2	0		insoluble			
3	0		insoluble			
4	3.4	530	0.00094	32 30	22 39	menthol, ginger, cloves burning, spicy, ginger
5 (+ 40% **4**)	2.2	1400	0.00036	60 46	10 24	menthol, ginger, cloves ginger, cloves > menthol
18	2.6	960	0.00052	4 10	82 48	biting, cloves > menthol burning, cloves > menthol
6		19	0.026	0	87	sour
Cyclohexene Analogs						
7		130	0.0038	54	23	menthol, mint, coconut
8	*d*	180	0.0027	38 0	21 25	menthol, mint, coconut > phenolic burning, menthol, coconut
9		380	0.0013	16	54	menthol, mint, coconut > phenolic
10	1.0	30	(0.017)[e]	0 0	62 22	 burning, menthol
11 (+25% **12**)		220	0.002	12	13	sour, menthol, medicinal
12		270	0.0019	0	34	sour, leafy, minty, rotten
13		125	0.0040	18	36	mint, licorice > medicinal
Open-chain Analogs						
14	>5[f]	120	0.0042	37 10	20 40	menthol, mint, phenolic, medicinal > sour burning, menthol, mint
15		240	0.0021	15	20	phenolic, medicinal > menthol
16		460	0.0011	11	27	menthol, coconut > chemical > leafy
17		300	0.0017	2	52	oily, leafy, rancid
Isomeric Pairs of Aromatic Oximes						
18	2.6	960	0.00052	4 10	80 48	biting > cloves > menthol burning, peppery, cloves, menthol
19	0		insoluble			
20	>5[g]	360	0.0014	15 20	50 40	burning > sour > menthol peppery, sharp
21	0		insoluble			
22	2.4		insoluble	10	40	burning
23	0.8		insoluble	90	10	

[a] Relative to solid dextrose as 1. [b] Intensity of solution (relative to 0.5*M* dextrose as 1)/molar concentration; divided by intensity of dextrose solution/0.5*M*. [c] Determined by linear extrapolation from actual intensities varying from 0.3 to 4.0. [d] Intensity of solid increases with time, from nearly tasteless to strongly burning. [e] Extrapolated from saturated solution, 0.004 molar, intensity 0.2. [f] Solid immediately very strong; burning, menthol. [g] Estimated; very strong.

The isomeric nature of aldoximes was determined simply and clearly from the nmr spectra by observing the difference in chemical shift between the NOH and CH=N signals in dimethylsulfoxide-d_6. This difference was stated to be $\cong 3$ for *syn* oximes and $\cong 4$ for *anti* oximes (Kleinspehn *et al.*, 1967). The wide applicability of this principle is seen in Table II, for 14 *syn* oximes and 4 *anti* oximes. The only borderline case was compound **13**, with a difference of 3.40. This was readily assigned to the *syn* isomer when the *trans* isomer with a difference of 4.18 was observed in the spectrum as a minor impurity (6%).

The cyclic compounds all were of necessity *trans* olefins, as in structure (**a**). The open-chain aldoximes (**14–16**) were *trans* in the same sense, judging by the characteristic chemical

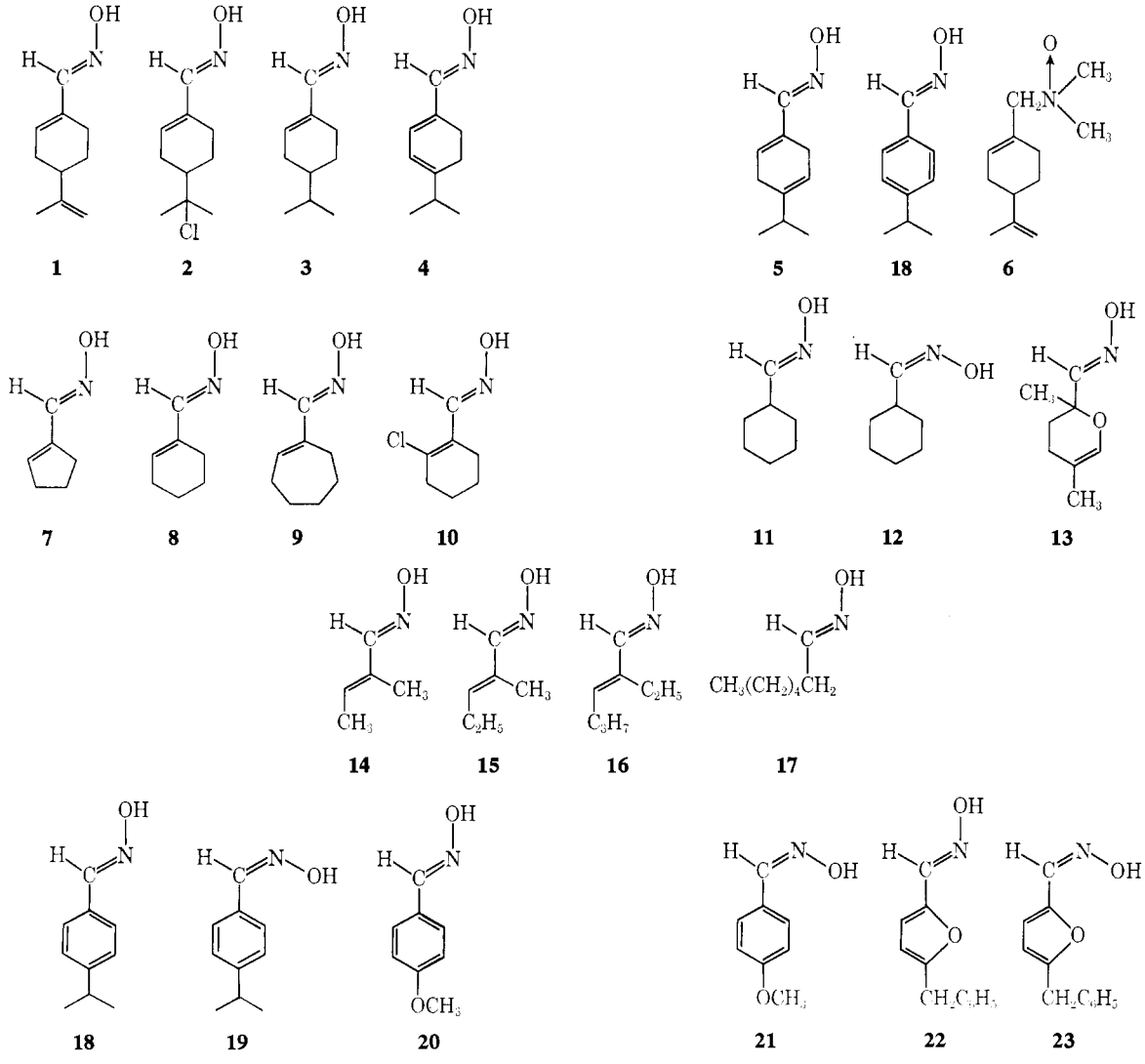

Figure 1. List of compounds tasted

shift near δ 9.3 (Büchi and Wüest, 1969) for the parent aldehyde CH=O. That there was no C=C isomerization to *cis* during the oximation step was evident from the vinyl protons on the β-carbon, which maintained the same splitting patterns and coupling constants in the oximes as in the respective aldehydes. The upfield shift of about 0.8 ppm on oximation was consistent for all the vinyl protons on a β-carbon.

EXPERIMENTAL

Taste Evaluation. Evaluation of overall taste intensity and characterization of the several basic tastes present was accomplished using standard psychophysical procedures. Testing was carried out in a facility designed expressly for the taste research and flavor evaluation. It included a preparation room and eight individual taste booths, complete air conditioning, controlled lighting, running water, and sinks for expectoration.

The same group of five or six individuals served as panel members for evaluation of all materials. Fairly complete information was available about each subject's performance on previous taste research experiments and the individuals were considered trained, reliable judges (Stone and Oliver, 1969).

Subjects received samples in three-digit coded beakers along with an identified reference sample (0.5*M* dextrose) and water and French bread sticks for rinsing. At each test session the subject also received the reference unidentified as a check on response variability.

The scoring technique was a modified magnitude estimation procedure. Each subject tasted a solution and indicated the perceived intensity relative to the reference; *i.e.*, half as strong, five times as strong. He was then asked to characterize the flavor by indicating the degree of sweetness, sourness, saltiness, bitterness, or any other perceived taste such that the total equaled 100. The final task was to indicate the presence or absence of aftertaste.

Results for each subject were compared to the panel averages and especially with response to the reference sample. If a subject exhibited unusual variability, *e.g.*, failing to properly score the reference ($\pm 10\%$), these data were excluded or the test repeated. In only three or four cases were these steps necessary.

For most materials, results were averaged for not more than one or two replications (10 to 18 evaluations per compound). However, compounds which possessed considerable sweetness were subjected to more exhaustive sensory analysis.

Occasionally solids were tasted, which presented unusual problems insofar as equal amounts of sample were concerned. Considerable care was taken to insure that subjects always received, and hopefully used, the same amount of sample each time. Results from these tests were considered only secondary to the data on compounds in solution.

Table II. Nmr Data

Compound	Oxime CH=N (δ, $CDCl_3$)	Oxime C=CH[a] (δ, $CDCl_3$)	Oxime δNOH-δCH=N (DMSO-d_6)	Parent Aldehyde CH=O (δ, $CDCl_3$)	Parent Aldehyde C=CH[a] (δ, $CDCl_3$)	δ Aldehyde − δ Oxime for C=CH
Cyclic						
1	7.71 s	6.05 br	3.02	9.43 s	6.80 br	0.75
2	7.71 s	6.05 br	2.99			
3	7.69 s	6.02 br				
4	7.77 s	6.09 d[b]	3.00	9.40 s	6.68 d[c]	
5	7.77 s	6.1[d]	2.97			
7	7.93 s	6.06 br	2.85	9.77 s	6.89 s	0.83
8	7.68 s	6.01 br	2.92	9.42 s	6.82 m	0.81
9	7.67 s	6.09 t	2.93	9.29 s	6.87 t	0.78
10	8.32 s		2.97			
11	7.32 d		3.10	9.63 s		
12	6.53 d		4.06	9.63 s		
13	7.42 s		3.40[e]	9.50 d		
Open-chain						
14	7.71 s	5.80 m		9.37 s	6.60 q × d	0.80
15	7.71 s	5.73 t		9.38 s	6.48 t × d	0.75
16	7.62 s	5.65 t	2.98	9.32 s	6.39 t	0.75
17	7.60 t		2.99			
Aromatic						
18	8.17 s	7.50 d	2.95			
19	7.38 s	7.88 d	4.10			
20	8.10 s	7.51 d	2.82			
21	7.30 s	7.92 d	4.01			
23	7.95 s					
24	7.45 s		4.23			

[a] Proton β- to C=N or C=O. [b] γ CH=C at δ 5.78 m. [c] Values of Kayahara *et al.* (1968), whose assignments of β- and γ-=CH's should be reversed. [d] γ CH=C at δ 5.51 br. [e] Assigned to *syn* isomer; for *anti* isomer of **13**, this value = 4.18; see Experimental.

Chemistry. PREPARATION OF OXIMES. Except where noted, aldehydes in aqueous 60% ethanol solution (7 ml per gram) were conventionally converted to oximes by treatment with hydroxylamine hydrochloride and sodium acetate, each in 15% molar excess. The solution was refluxed for 1 to 2 hr, the ethanol was removed *in vacuo*, and the oxime was extracted with ether or with dichloromethane. The extracts were washed with aqueous sodium bicarbonate, dried, evaporated, and the residual oxime was recrystallized or distilled.

THIN-LAYER CHROMATOGRAPHY (TLC). Except for **11**, the oximes were all homogeneous on silica gel F (Brinkmann) with benzene-ethyl acetate (5 to 1), including the mixture of **4** and **5**. The α,β-unsaturated and aromatic oximes were detected under ultraviolet light; all could be detected with iodine.

NMR SPECTRA. These were run routinely in chloroform-*d* solutions with 2% tetramethysilane as internal standard (δ 0.00) at 60 MHz. Oximes were also run in dimethylsulfoxide-d_6 with internal tetramethysilane for determination of the difference δ_{NOH}-$\delta_{CH=N}$ (Table II). Signals are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Integrated signal ratios were determined routinely and were as expected from the structure assignments.

4-ISOPROPENYL-1-CYCLOHEXENE-1-CARBOXALDEHYDE *syn*-OXIME (PERILLARTINE, **1**). The racemate was obtained from Aldrich Chemical Co., Inc., and from Yukigosei Kogyo Co., Ltd., Tokyo. A sample of the (−)-form was a gift from Robeco Chemicals, Inc., New York, $[\alpha]_D^{23°}$ − 128.3° (*c* 1, 95% ethanol).

DL-4-(2-CHLORO-2-PROPYL)-1-CYCLOHEXENE-1-CARBOXALDEHYDE *syn*-OXIME (**2**). DL-Perillartine (10 g) was dissolved in 20 ml of concentrated hydrochloric acid. The yellow solution after 10 min formed a thick suspension. Water (400 ml) was added, and the solid was collected and washed free of chloride ion. It weighed 8.3 g (68%), m.p. 130–131° C. Recrystallization from ethanol-water raised the m.p. to 134–135 C.

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.6; H, 7.99; Cl, 17.6; N, 6.94. Found: C, 59.7; H, 7.98; Cl, 17.9; N, 6.90.

DL-4-ISOPROPYL-1-CYCLOHEXENE-1-CARBOXALDEHYDE *syn*-OXIME DL-PHELLANDRAL OXIME (**3**). A sample of racemic phellandral was a gift from International Flavors and Fragrances, Inc. It was also synthesized from 4-isopropylcyclohexanone. The literature procedure (Frank *et al.*, 1949) was modified by reduction of 4-isopropyl-1-cyano-1-cyclohexene directly to phellandral with diisobutylaluminum hydride in hexane solution, as described by Tanabe and Yasuda (1970). The oxime melted at 70–72° C (Frank *et al.*, 1949; m.p. 76–77° C).

DL-4-ISOPROPYL-1,3-CYCLOHEXADIENE-1-CARBOXALDEHYDE *syn*-OXIME (**4**). A sample obtained by isomerization of **1** with boron trifluoride in benzene solution (Acton *et al.*, 1970; Hauser and Hoffenberg, 1955) melted at 51–58° C and showed no **1** or 1,4-diene by nmr. A solution of 2.59 g in 50 ml of 1*M* sodium hydroxide was clarified by filtration, chilled to 5° C, and neutralized to pH 5 with 3*M* hydrochloric acid. The precipitate was collected, triturated with water, and dried (2.10 g), m.p. 54–57° C, identical to **1** on tlc.

Anal. Calcd. for $C_{10}H_{15}O$: C, 72.7; H, 9.15; N, 8.48. Found: C, 72.8; H, 9.15; N, 8.45.

4-ISOPROPYL-1,4-(1,3)-CYCLOHEXADIENE-1-CARBOXALDEHYDE *syn*-OXIME (**5,4**). By the same procedure, except that the boron trifluoride treatment was halted after 20 min, the mixture of 1,4- and 1,3-dienes (60:40, respectively) was obtained, m.p. 59-60° C, free of **1** according to nmr.

DL-*N*,*N*-DIMETHYL-[4-(ISOPROPENYL)-1-CYCLOHEXENYL]-

METHYLAMINE. DL-Perilla alcohol (Givaudan) was converted to the crude, unstable *O*-*p*-tolylsulfonate in 25% yield, by the procedure (Cristol and Nagpal, 1961) for the methylsulfonate of 1-cyclohexenylmethanol. A major byproduct was the quaternary pyridinium tosylate salt, a water-soluble solid. The product itself was an oil, characterized in the nmr by signals at δ 5.82 (ring CH=C; shifted from 5.72 for perilla alcohol) and 3.99 s (C=C—CH_2X; same as CH_2OH of perilla alcohol), in addition to the usual isopropenyl signals; weakness of tosyl signals at 7.92 d and 7.42 d (*p*-C_6H_4, J = 8.0 Hz) and 2.49 s (aryl CH_3) suggested this product may have been largely perillyl chloride. Treatment in benzene solution with dimethylamine, by the procedure for cycloocten-3-yldimethylamine (Cope and Estes, 1950) afforded the dimethylamine in 57% yield, after acid washing to remove nonbasic impurities and short path distillation at 13 mm; nmr δ 5.60 (ring C=CH), 4.72 d ($C=CH_2$), 2.75 s (C=C—CH_2N), 2.15 s (NMe_2), 1.74 d (C=C—CH_3).

DL-*N*,*N*-DIMETHYL-[4-(ISOPROPENYL)-1-CYCLOHEXENYL]-METHYLAMINE *N*-OXIDE (**6**). The above dimethylamine was converted to the *N*-oxide with 30% hydrogen peroxide in ethanol, by the procedure for cycloocten-3-yldimethylamine oxide (Cope and Bumgardner, 1956) and for cyclooctyldimethylamine oxide (Cope *et al.*, 1953). After the oxidation of amine was complete and the excess peroxide was decomposed, concentration of the solution afforded the oxide as a partly crystalline residue, presumably a hydrate. The substance was readily soluble in either water or chloroform. The nmr spectrum disclosed the presence of 1.5 moles of water: δ 5.97 (ring C=CH), 4.74 m ($C=CH_2$), 4.03 broad (H_2O, exchangeable; integrated for 3 H's), 3.82 s (C=C—$CH_2N\rightarrow O$), 3.08 s (NMe_2), 1.75 d (C=C—CH_3). Striking downfield shifts of the CH_2NMe_2 group, about 1 ppm, were diagnostic for *N*-oxidation. A shift (about 0.4 ppm) of the ring C=CH on *N*-oxidation was also observed, downfield to a resonance nearly coincident with that of perillartine.

1-CYCLOPENTENE-1-CARBOXALDEHYDE *syn*-OXIME (**7**). 1-Cyano-1-cyclopentene (Wheeler and Lerner, 1956) from cyclopentanone was reduced directly to 1-cyclopentene-1-carboxaldehyde (Brown *et al.*, 1950; Klinck and Stothers, 1966) (32% yield), b.p. 68–70° C (35 mm) with diisobutylaluminum hydride in hexane solution, as described by Tanabe and Yasuda (1970). The crude oxime (70%) was distilled at 70–72° C (2 mm) and recrystallized from pentane at 5° C, m.p. 34–37° C.

Anal. Calcd. for C_6H_9NO: C, 64.8; H, 8.16; N, 12.6. Found: C, 64.6; H, 8.24; N, 12.4.

1-CYCLOHEXENE-1-CARBOXALDEHYDE *syn*-OXIME (**8**). Prior to development of the diisobutylaluminum hydride reduction method (as for **7**), 1-cyclohexene-1-carboxaldehyde was prepared (Klinck and Stothers, 1966) from 1-chloro-1-cyclohexene. The oxime (**8**) melted at 99–100° C (Treibs and Helbig, 1959; m.p. 98–99° C); a sample for tasting was recrystallized from hot water (2 g in 100 ml).

The preferential existence of the *syn*-oxime was demonstrated by unsuccessful attempts at isomerization to the hypothetical *anti* form. Neither conversion to the hydrochloride salt, by passing hydrogen chloride into a benzene solution, followed by regeneration with sodium hydroxide, nor treatment with boron trifluoride in benzene followed by sodium bicarbonate (Hauser and Hoffenberg, 1955) effected any change in the *syn* oxime.

1-CYCLOHEPTENE-1-CARBOXALDEHYDE *syn*-OXIME (**9**). This was obtained from cycloheptanone through 1-cyano-1-cycloheptene, as for **7**. The oxime was distilled at 70–76° C (0.2–0.3 mm) and recrystallized from pentane, m.p. 41–42° C.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.0; H, 9.41; N, 10.1. Found: C, 69.0; H, 9.58; N, 10.1.

1-CHLORO-1-CYCLOHEXENE-1-CARBOXALDEHYDE *syn*-OXIME (**10**). M.p. 107–108° C (Benson and Pohland, 1965; m.p. 108.0–108.5° C), could be dissolved in water (up to 10 mg in 100 ml), but since the solution was nearly tasteless, it was tasted as the solid.

CYCLOHEXANECARBOXALDEHYDE *syn*-OXIME (**11**). This was an oil, R_f 0.7 in benzene ethyl acetate (3:1), which could not be separated from some of the crystalline *anti* oxime, R_f 0.6, and consequently was tasted as a nearly equilibrated (Karabatsos and Taller, 1968) mixture (*syn*:*anti*, 75:25, by nmr).

CYCLOHEXANECARBOXALDEHYDE *Anti*-OXIME (**12**). This was separated by adding pentane to the mixture and chilling, and the crystals were recrystallized from pentane, m.p. 90–91° C, softening at 80° C (Zelinsky and Gutt, 1907; m.p. 90–91° C; this *anti* oxime was mistakenly designated *β-syn*, in line with the general misconception of this period). There was only 5–10% conversion to the *syn* isomer **13** on storage of a dimethylsulfoxide solution for 24 hr.

3,4-DIHYDRO-2,5-DIMETHYL-2*H*-PYRAN-2-CARBOXALDEHYDE *syn*-OXIME (**13**). This was distilled at 71–72° C, 0.5 mm (Stoner and McNulty, 1950; b.p. 92–95° C, 3 mm). The nmr spectrum (*cf.* Table II) disclosed the presence of 6% of the *anti* isomer, δ ($CDCl_3$) 6.71 (CH=N), $\delta_{NOH} - \delta_{CH=N}$ (DMSO-d_6) = 4.18.

TIGLIC ALDEHYDE, *syn*-OXIME (**14**). Crystallized after distillation (45% yield), b.p. 80–82° C (12–15 mm) and was recrystallized from pentane, m.p. 35–38° C (Wiley and Wakefield, 1960; m.p. 42–43° C), R_f 0.38 on tlc.

trans-2-METHYL-2-PENTENAL, *syn*-OXIME (**15**). The aldehyde (Haüsermann, 1951), containing 2% of the *cis*-isomer, was converted to crude oxime, m.p. 43–47° C (92% yield), which was recrystallized from pentane, m.p. 47–48° C (Hesse and Maurer, 1962; m.p. 48–49° C); maximum water solubility was 35 mg/100 ml.

trans-2-ETHYL-2-HEXENAL, *syn*-OXIME (**16**). The aldehyde (Haüsermann, 1951; Nielsen and Houlihan, 1968) afforded crude oxime (94%) which crystallized at 5° C, and was recrystallized from cold pentane, m.p. 20–23° C; maximum water solubility was 16 mg/100 ml.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.7; N, 9.92. Found: C, 67.8; H, 10.9; N, 9.84.

n-HEPTALDEHYDE, *syn*-OXIME (**17**). This was obtained from Eastman, m.p. 52–53° C, R_f 0.6 on tlc; maximum water solubility was 30 mg/100 ml.

AROMATIC OXIMES. *p*-Isopropylbenzaldehyde and *p*-anisaldehyde were converted to the *α-syn*-oximes (**18** and **20**, respectively) and then to *β-anti*-oximes (**19** and **21**) by a detailed procedure (Schoenewaldt *et al.*, 1968). Melting points and R_f's were as described (Pejkovic-Tadic *et al.*, 1964) and nmr data in chloroform-*d* (as in Table II) were identical to those given (Pejkovic-Tadic *et al.*, 1965) in tetrahydrofuran (the designations α- and β- are correctly correlated with *syn* and *anti* isomers, respectively, in these references; it is important to remember that these designations were incorrectly reversed in the early literature).

5-Benzylfurfural (Gilman and Dickey, 1930) was similarly converted to the *α-syn*-oxime (**22**), m.p. 98–99° C (Fenton and Robinson, 1909; m.p. 97–99° C), and then to the *β-anti*-oxime (**23**), m.p. 124–126° C (Fenton and Robinson, 1909; m.p. 124° C). These oximes (**22** and **23**) were sparingly soluble in water as stated (Gilman and Dickey, 1930), but contrary to the report, the very dilute solutions were tasteless.

Table III. Some Compounds at Varied Concentrations

Compound	Concentration (mole/l.)	Intensity of Solution Compared to 0.5M Dextrose	Relative Intensity Per Mole of Compound Relative to Mole of Dextrose	Observed Flavors (percent of total[a])				
				Sweet	Bitter	Sour	Menthol Mint Coconut	Phenolic Medicinal
1	0.0036	2.8	4300	64	19	5	3	0[b]
	0.0012	1.1	5000	62	14	19	2	0
	0.0010[c]	0.36	1560	74	10	4	2	0
7	0.020	5.0	167	57[d]	40	2	0	0
	0.010	2.9	120	61[d]	12	0	3	0
	0.0050[c]	1.0	110	50	20	10	18	0
8	0.010	5.9	330	40[d]	22	0	14	8
	0.0050	1.1	147	52	5	12	30	0
	0.0025	0.8	225	51	19	4	12	0
	0.0020	0.2	55	37	15	7	0	8
14	0.020	3.4	117	55	4	15	18	5
	0.010	2.0	111	51	18	7	10	13
	0.0050[c]	0.8	86	38	10	10	11	30
	0.0020[c]	0.4	140	36	30	11	20	0

[a] Totals are often less than 100%, since minor flavors noted are omitted from the table. [b] A gingery flavor was also noted at this concentration. [c] Averages of two separate determinations by the panel at the same concentration. The Relative Taste Intensities (for solutions) in the Tables were averages of all the separate determinations. [d] A burning taste was also noted at this concentration.

RESULTS

Results of the structure-taste evaluations are summarized in Table I. Relative Taste Intensity for the solids was determined by direct comparison with solid dextrose. For the compounds in solution, Relative Taste Intensity was calculated from:

$$\frac{\text{Taste Intensity of Soln.}}{\text{Molarity}} \text{ divided by } \frac{\text{Taste Intensity of Dextrose Soln. } (\cong 1.0)}{\text{Molarity of Dextrose } (0.5M)}$$

The numbers listed are averages from determinations at several concentrations, except for **6**, **11**, **12**, and **17**, where the tastes were not sweet, and responses by the panel at a single concentration were deemed sufficient. The Solution of Unit Intensity is the molar concentration of the compound at which the taste intensity is equivalent to that of 0.5M dextrose. This was determined by extrapolation from solutions which departed from unit intensity, by factors not greater than 3 or 4. The extent of perceived sweetness or bitterness was recorded under Observed Tastes as percentages of the total taste sensation. The other tastes observed are simply recorded, and may represent either major or minor components. The compounds of greatest interest seemed to be the cyclopentene and cyclohexene aldoximes (**7** and **8**) and tiglic aldoxime (**14**); more responses were obtained for these compounds, and the detailed data are given, along with those for perillartine (**1**), in Table III.

Compounds **1** through **6** are those which retained the carbon skeleton of perillartine. Solutions of perillartine (**1**) had definite taste, though limited to moderate intensity by the very low water solubility. Compared in solution with dextrose, however, on an equimolar basis, the taste was about 3000 times stronger than dextrose. These results are in good agreement with those reported (2000 times sucrose) by Furukawa and Tomizawa (1920). A 0.0016M solution of perillartine had a taste intensity equivalent to 0.5M dextrose. Solutions were measured over a range of 0.00010M up to 0.00036M, which at room temperature was near saturation. Sweetness was accompanied by less than 20% bitterness, and faint sour and gingery notes. Almost identical qualities were shown by perillartine tasted as the solid. The mild taste of the solid (only 2.5 times the intensity of solid dextrose) was due to its low solubility. DL-Perillartine was generally used in this work. A sample of (−)-perillartine was indistinguishable from the racemate on the basis of a limited number of tests.

The lack of taste for the HCl adduct (**2**) of perillartine (Acton *et al.*, 1970; Furukawa and Tomizawa, 1920) and for phellandral oxime (Frank *et al.*, 1949) (**3**) has been reported, and is easily confirmed, either with the dry solids or with the water used in attempts to dissolve them. This is doubtless owing to their complete insolubility. Prolonged exposure of **2** to water gives sourness, due to decomposition with loss of HCl.

The diene isomers of perillartine, **4** and **5**, retained borderline solubility and showed relatively strong tastes in solution. The proportion of sweetness to the overall taste qualities decreased by about one-half in going from perillartine to the 1,3-diene (**4**), and the spicy, menthol notes increased. The 1,4-diene (**5**) could not be obtained free of about 40% of **4**, and was consequently tasted as a mixture. It appeared that some sweetness was restored with the unconjugated diene (**5**). The parent aldehyde of **5** has recently been found (Varo and Heinz, 1970) in fresh cumin seeds as perhaps the major naturally occurring aldehyde. The completely aromatic analog, *p*-isopropylbenzaldehyde *syn*-oxime (**13**), showed very little sweetness and was almost entirely bitter.

The amine oxide (**6**) retained intact the terpene moiety of perillartine, but acquired easy water solubility by this change in functional group. The taste was almost completely bitter. Not only was sweetness entirely lost, but the loss in taste intensity was significant. The intensity of **6** was only 1/10 to 1/100 that of nearly all the oximes studied. This suggested that the oxime functional group may be associated with both sweetness and strong taste intensity.

Compounds **7**, **8**, and **9** constituted a simple series in which the alicycle ring size was varied, retaining olefinic unsaturation conjugated with the oxime. Solubilities were much easier than with perillartine. The upper limit of solubility for the cyclohexene aldoxime (**8**) was about 0.02M, at which level both **7** and **8** gave strong taste responses, with slight burning sensations. The upper limit of solubility for the cycloheptene (**9**) was about 0.005M. In solutions of unit

intensity (*i.e.*, intensity equivalent to 0.5*M* dextrose) there was no burning. The cyclopentene aldoxime (**7**) was predominantly sweet, though less so than perillartine. Sweetness fell off as the ring size was increased, while at the same time bitterness increased. Menthol, mint, and coconut flavors were noted consistently in all three, with a slightly phenolic quality appearing in **8** and **9**. When solid **8** was tasted, the burning, menthol, coconut sensations overwhelmed other flavors.

The oxime (**10**) with the vinyl chloride on the β-carbon was much less soluble than its analog **9**. Maximum solubility was 0.004*M*, at which level the taste was weakly bitter; solid **10** was burning, bitter, and without sweetness. Loss of solubility with the β-chlorine was predictable, but decrease in taste intensity and loss of sweetness suggests interaction with the receptor site may be blocked by the bulky chlorine atom. Upon saturation of the olefinic bond (of **8**), the cyclohexane *syn*- and *anti*-aldoximes (**11** and **12**) retained taste intensity, but lost sweetness almost entirely, and the overall taste was unpleasant. The oxime (**13**) of crotonaldehyde dimer has a hetero ring oxygen in place of the α,β-unsaturation (of **1** or **8**); though sweetness was low, the taste qualities were largely pleasant.

A series of open-chain, α,β-unsaturated aldoximes (**14–16**) showed trends much like **7–9**, *i.e.*, strong taste intensity, with moderate sweetness which fell off as the carbon chain increased. A certain degree of bitterness remained about the same from **14** to **16**. The usually perceived menthol, mint qualities were accompanied by stronger medicinal, chemical notes than in the cyclic series. Though water solubility decreased from high solubility with tiglic aldoxime (**14**) to a limiting solubility of 0.003*M* for **16**, relative taste intensity increased through the series. Again, loss of the α,β-unsaturation (in **17**) caused loss of sweetness without loss of perceived taste intensity. The taste of *syn*-heptaldoxime was predominantly unpleasant.

Three pairs of isomeric *syn* and *anti* oximes of aromatic aldehydes were prepared. *p*-Isopropylbenzaldoximes (**18** and **19**) were chosen to complete the series **1**, **3**, **4**, and **18**; *p*-anisaldoximes (**20** and **21**) and 5-benzylfurfuraldoximes (**22** and **23**) were chosen to test earlier reports of sweetness. The *anti* forms of both benzaldehyde derivatives were insoluble and tasteless. The *syn* forms had appreciable water-solubility, but were strongly burning and bitter in taste. Even *syn-p*-anisaldoxime showed little sweetness. Both furfural derivatives were practically insoluble. Despite the previous report, solutions of **22** or **23** with discernible taste could not be prepared. The dry solids, however, did show some taste. The *syn* isomer, like **18** and **20**, was burning and bitter. The solid *anti* isomer was weakly sweet. It may not be concluded from these compounds that sweetness of oximes is simply related to *syn-anti* isomerism. Beyond this, 5-benzylfurfural *anti*-oxime has not been pursued as a screening lead because of its insolubility and low taste response.

DISCUSSION

A number of conclusions can be drawn from these tests regarding the taste properties of oximes, as well as in regard to the more general problem of structure-taste relationships. There are numerous references to structure-flavor studies; however, the results are based almost entirely on secondary taste information. Unfortunately, one cannot rely on such data in attempting to formulate a reasonable structure-taste hypothesis. Shallenberger and Acree (1967) proposed that perceived sweetness is due to intermolecular hydrogen bonding between the glycol unit of sugar and the taste bud receptor site. Further, the glycol should be considered as consisting of an AH and a B component, where A and B are electronegative atoms with a proton attached to one of these (A) by a covalent bond. These authors presented a series of examples in support of their hypothesis, and included compounds with other functional groups. Our interest in this hypothesis was based on the AH,B system which also exists in the oxime structure. The results of our experiments suggest that the AH,B concept represents only a first approximation. Certainly the AH,B system is required in the structure; however, other structural characteristics associated with the carrier group may completely mask any AH,B effect.

As a class of compounds, the oximes exhibited relatively strong taste intensities. This is true even if one discounts the linear extrapolations which were made for comparison with the dextrose reference. The loss of intensity was striking with the only nonoxime that was studied, the amine oxide (**6**). The only other compound with a relative taste intensity less than 100, compared in solution to dextrose, was the β-chlorooxime **10**. Here it seemed possible that the bulky chlorine might have blocked interaction of the AH,B function with the receptor site. The tastelessness of some oximes (*e.g.*, **2** and **3**) was attributed to their practically complete insolubility. Water solubility of the compounds, of course, is of prime importance. It was notable with the oximes that a very low solubility often sufficed to give a definite taste to the solution. This is advantageous for any potential use as a food additive. Some of the most interesting compounds, *e.g.*, perillartine itself, showed only borderline solubility. To some extent it appeared to be at concentrations near the point of saturation at which the compounds showed appreciable tastes, and the more soluble compounds seemed to have less intense tastes, on a molar basis. Nevertheless, it is clear that oximes as a class of compounds show high taste intensities, based on moles of compound in solution.

For sweetness in oximes, presence of the conjugated double bond appeared to be essential. Saturated oximes showed little or no sweetness; they had a generally unpleasant flavor, though perceived intensity was not significantly altered. Within two series of α,β-unsaturated oximes where lipophilicity was increased, by increasing ring size (compounds **7**, **8**, **9**) or chain length (compounds **14**, **15**, **16**), perceived intensity was also increased. To some extent bitterness was also increased, but sweetness was decreased. The open chain compounds showed slightly less sweetness and slightly more phenolic or medicinal flavor than the alicyclic compounds. Several factors remain unexplored: the effect of *syn* and *anti* isomerism in similar aldoximes lacking an α-substituent; the effect of varying the *trans* geometry of open-chain olefins; and the effect of analogous methyl ketoximes.

Aromatic aldoximes appear not to be of much interest, even when structurally similar, like **18**, to perillartine. *Anti* isomers were completely insoluble, and *syn* isomers were predominantly burning and bitter. The weak sweet taste observed with solid 5-benzylfurfural *anti*-oxime (**23**) showed that sweetness cannot necessarily be correlated with *syn*-isomerism.

Based on our present investigations, we concluded that systematic study of a particular class of chemicals can provide meaningful information about structure-taste relationships. It is also concluded that no one aspect of a molecule is the sole determinant of taste quality. Such factors as water-lipid solubility, level of unsaturation, and presence and location of functional groups act in concert with the receptor site to affect the behavioral response of the individual to that stimulus. Our investigations into these problems are continuing.

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