immediately after the completion of the decomposition of 2. For this purpose, solvent system B was employed in the absence of additives, solvent system D when cysteine had been added, and solvent system C with other additives.

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Structure-Taste Relationship of Perillartine and Nitro- and Cyanoaniline Derivatives

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The relationship between structure and taste potency of perillartine and its analogues was investigated quantitatively by physicochemical parameters and regression analysis. The results indicated that the hydrophobicity estimated from the 1-octanol/water partition coefficient and the molecular widths from the bond axis connecting the oxime carbon and alicyclic ring are important, regardless of whether the taste is sweet or bitter, so far as the taste potency is concerned. The SAR for the sweet/bitter ratio was not established quantitatively, but the molecular width and thickness and the position-specific electronic effect seem to delineate the ratio qualitatively; i.e., in principle, the wider and/or the thicker the molecule, the more bitter the taste. Comparatively, the QSAR of 5-nitro- and 5-cyanoaniline sweetners was formulated to show the insignificance of the hydrophobicity within the compounds investigated but the importance of the steric dimensions in determining the activity.

Among the sweet compounds hitherto known,[1] the perillartines are a class in which the activity has been estimated quantitatively in terms of both the taste potency relative to a standard sucrose solution and the sweet/bitter ratio.[2] Thus, the data promote attempts to correlate the relationship between the structure and the sweet/bitter ratio, as well as that between the structure and taste intensity. Whether the sweet materials bind to a common receptor on the tongue or there are different receptor sites for different groups of sweetners has been the subject of extensive studies, as well as the problem whether the receptors for the sweet and bitter taste are common or multiple.

The quantitative structure–activity analysis has been shown in certain cases to lead to a better understanding of the mode of interaction of biologically active molecules with their receptor, as well as the nature of the receptor site.[3] To my knowledge, however, the 2-substituted 5-nitroanilines are the only class of the sweetners whose potency has been analyzed in this sense.[4,5] In the plant hormone area, Iwamura et al. have correlated the variations in the activities of cytokinins and anticytokinins with the hydrophobic parameter derived from the 1-octanol/water partition coefficient and the steric parameter for the maximum width of a substituent from the bond axis.[6-8] Through these studies, the new steric parameters, the STERIMOL parameters recently developed by Verloop et al.,[9] have played a key role for the correlations. These results and those reported by Verloop et al.[9] thus prompted me to analyze the taste characteristics of sweetners in a manner similar to that used for the analyses of cytokinin and anticytokinin activities. In this article are reported the results on two classes of sweetners, perillartines and 2-substituted 5-nitro- and 5-cyanoanilines. Even if different classes of sweetners exert their effect at different receptors, it is more meaningful for designing new tastants to try to seek for the common peculiarities between different classes of compounds than to restrict the analyses within a congeneric series.

Methods

Activity data were taken from literature reported by Acton et al.[2] for perillartines and those reported by Blanksma et al.[10] and Verkade et al.[11] for aniline derivatives.

The STERIMOL parameters[9] were used to evaluate the steric dimensions of compounds. The L parameter expresses the length of the substituent R_1 along the bond axis which connects R_1 and the oxime carbon in perillartines. R_1 is the rest of the molecule from which the common oxime end is subtracted. In aniline derivatives, it is the length of the whole substituted benzene moiety along the bond axis between C_5 and the N atom of nitro or C atom of the cyano group. The W_l, W_r, W_u, and W_d are the molecular width in the directions perpendicular to the L axis and rectangular to each other. W_l in the perillartine series is taken as the width in the direction to which the 4 substituent extends in the fully extended (staggered) conformation, and the $C_1{=}C_2$ double bond is assumed to exist in this direction. In the nitro- and cyanoaniline series, it directs to the same side as the amino

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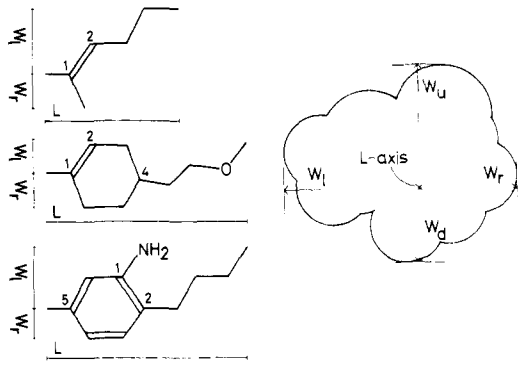


Figure 1. Schematic representation of the steric parameters L, W_l, W_r, W_u, and W_d.

group exists, and the 2 substituents are assumed to extend to this direction. W_r is the width in the direction opposite to W_l. W_u and W_d are the widths upward and downward, respectively, of the molecule when one views the molecule from the basic end along the L axis, locating the W_l to the left. These W parameters correspond to the original B_n (n = 1–4) parameters reported by Verloop et al.[9] and are shown schematically in Figure 1.

In aniline derivatives, the dihedral angle between the O–C_α bond of the 2-alkoxy substituent and the benzene ring was taken as 0°, taking the coplanarity due to resonance effect into consideration. The angle between the $C_{1'}$–$C_{2'}$ bond of the 2-alkyl substituent and the benzene ring was taken as 45° to minimize the steric constraint.

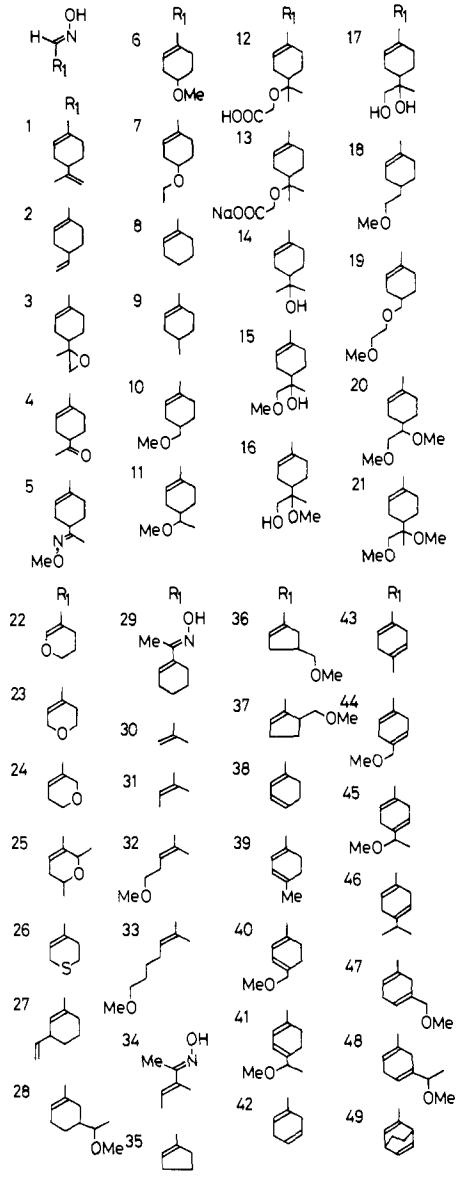
The conformations of the cyclohexenyl, cyclohexadienyl, and cyclopentenyl moieties of perillartines were calculated geometrically using the covalent radii and bond angles of the Corey–Pauling–Koltan atomic models, based on which the STERIMOL program was devised. Consequently, the torsion angle between the C_1=C_2 and C_3–C_4 bonds of cyclohexene was calculated to be 13.24°, that between C_2–C_3 and C_4–C_5 56.27°, and that between C_3–C_4 and C_5–C_6 73.03° in the half-chair form. Cyclohexa-1,4-diene was calculated to be nearly planar. Cyclohexa-1,3-diene and cyclopentene can not be exactly built from normal sp^3 and sp^2 carbons but were approximated by these in the planar conformation. When an asymmetric carbon occurs in the substituent, i.e., in the case of racemate, the steric parameter which concerns that center was expressed by the average value of the R and S configurations.

The hydrophobicity of the compounds, log P, where the P is the 1-octanol/water partition coefficient of a whole molecule, was estimated using the additive–constitutive nature as below. For the perillartine series, log P(RCH=NOH) = log $P(CH_3CH{=}N\text{-}OH)$[12] – $\pi(CH_3)$[13] + π(R), where π(R) = log P(RH) – log $P(H_2)$[14]. The log P for cyclohexene was taken from the literature.[12] The π values relative to the CH_2 of the ether and thioether linkage were estimated as log P(EtOEt)[12] – log $P(EtCH_2Et)$[12] and log P(EtSEt)[15] – log $P(EtCH_2Et)$,[12] respectively. The π values of other structural units were taken from the literature.[13] The log P values for the aniline derivatives were evaluated according to the method developed by Fujita.[16]

Results

Perillartines. The activity, log A, was expressed by the logarithm of the taste potency,[2] irrespective of sweetness and bitterness; i.e., it is reportedly the measure of taste intensity relative to that of sucrose on a mole/mole basis but not the taste quality.[2] Table I lists the data and the substituent parameters used. The electronic effect directed to the common, basic oxime moiety is considered to be constant through this series of compounds.

Chart I



Of the various combinations of the steric and other substituent parameters as independent variables, eq 1 gave

$$\log A = 0.63 \log P(\pm 0.31) + 0.19L(\pm 0.10) - 0.48W_l(\pm 0.18) - 0.62W_u(\pm 0.24) + 2.87(\pm 0.78) \quad (1)$$

$$n = 38,\ r = 0.91,\ s = 0.32$$

the best correlation. In eq 1 and the following equations, n is the number of compounds included in the analysis, r is the multiple correlation coefficient, and s is the standard deviation. The figures in parentheses are the 95% confidence interval.

The positive coefficient of the log P term indicates that the high hydrophobicity enhances the taste potency. The correlation is not improved by the addition of a $(\log P)^2$ term. As to the steric dimensions, eq 1 shows that the longer the molecule in the L direction, the higher the activity. The addition of the L^2 term did not improve the correlation. The negatively large coefficient of the W_l and W_u terms indicates that the molecular width and thickness are detrimental to the taste intensity. Since the W_d values are nearly constant through the series of compounds, the W_d term does not enter into the correlation. In contrast, the insignificance of the W_r term, in spite of the wide variation in its value from 3.0 to 6.0, is noteworthy. Table

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Table I. Taste Potency and Physicochemical Parameters of Perillartine Derivatives[a]

no.	log A obsd[c]	log A calcd. by eq 1	Δlog A	log (sweet/bitter)[b]	log P	L	W_l	W_u	W_r	W_d
1	2.57	2.83	−0.26	0.38	2.58	8.52	3.13	2.85	3.42	1.99
2	3.06	2.65	0.41	0.70	2.28	8.69	3.19	2.84	3.42	1.99
3*	1.70	1.35	0.36	0.81	1.10	8.64	3.02	3.86	3.49	2.11
4	1.08	1.41	−0.33	0.22	0.32	8.52	3.13	2.85	3.41	1.98
5*	1.90			0.44		10.89	3.13	2.85	3.52	1.98
6	0.90	1.19	−0.29	0.21	0.60	8.41	3.13	3.45	3.41	1.98
7	1.20	1.69	−0.49	0.21	1.10	9.39	3.13	3.45	3.41	1.98
8	1.74	1.90	−0.16	0.40	1.78	6.30	3.13	2.85	3.41	1.98
9	2.40	2.25	0.15	−0.10	2.08	7.26	3.18	2.85	3.41	1.98
10	1.72	2.00	−0.28	0.38	1.10	9.36	3.14	2.94	3.41	1.98
11	1.90	1.99	−0.09	0.40	1.40	9.36	3.14	3.26	3.56	2.10
12*	1.98	−0.07	2.05	0.15	−0.08	10.34	4.08	4.64	3.73	2.21
13*	1.00	−1.78	2.79	NS[b]	−4.08	11.16	3.67	3.91	3.73	2.21
14	0.90	1.32	−0.42	−0.66	0.88	8.56	3.14	3.56	3.56	2.10
15	0.60	0.67	−0.07	−1.05	−0.10	10.67	3.33	4.11	3.56	2.10
16	1.04	0.76	0.28	−1.40	−0.10	9.36	3.04	3.79	3.62	2.22
17*	1.48	0.34	1.14	−1.15	−0.92	9.37	3.14	3.56	3.56	2.10
18*	T	1.74			1.60	10.67	3.35	4.09	3.41	1.98
19*	I	0.40			0.10	12.76	4.21	4.70	3.41	1.98
20	0.90	1.12	−0.22	NS	0.42	10.67	3.53	3.76	3.54	2.11
21	1.70	1.12	0.58		0.72	10.67	3.51	4.08	3.63	2.22
22	0.48	0.36	0.12	0.07	−0.72	6.30	3.05	2.86	3.37	1.86
23	0.18	0.42	−0.24	NS	−0.72	5.51	3.05	2.53	3.41	1.97
24	0.30	0.40	−0.10	−1.52	−0.72	6.15	3.16	2.67	3.01	1.72
25	1.00	0.90	0.10	NS	−0.16	7.12	3.02	2.84	4.40	2.11
26	1.30	1.03	0.27	NS	0.34	6.05	3.25	2.62	3.43	2.03
27	2.24	1.83	0.41	−0.39	2.28	7.30	4.05	3.07	3.41	1.98
28	1.45	1.63	−0.18	−1.40	1.40	7.98	3.12	3.42	5.96	2.00
29*	2.61	2.09	0.52	NS	2.08	6.30	3.13	2.85	3.41	1.98
30	0.90	1.14	−0.24	−0.08	0.37	4.29	3.08	2.08	3.01	1.71
31	1.60	1.67	−0.09	0.84	0.87	5.10	3.13	1.91	2.94	1.90
32	0.60	0.88	−0.28	−1.30	0.39	8.27	5.42	1.91	2.94	1.92
33	1.23	1.20	0.03	−0.82	1.39	10.32	6.87	1.91	2.94	1.93
34*	2.15	1.88	0.28	NS	1.17	5.10	3.13	1.91	2.94	1.90
35	1.74	2.14	−0.40	0.84	1.37	5.62	3.04	1.91	2.94	1.90
36	1.38	1.41	−0.03	0.64	0.69	8.04	3.04	3.14	4.81	3.12
37	1.52	0.94	0.58	−0.12	0.69	5.62	3.04	3.16	6.18	3.12
38	1.95	2.17	−0.22	0.52	1.48	6.06	3.09	2.08	3.01	1.71
39	2.18	1.87	0.32	0.23	0.78	6.87	3.08	2.11	3.02	1.73
40*	NI	1.85			0.80	8.87	3.38	2.51	3.12	1.98
41	2.13	2.00	0.13	0.97	1.10	8.87	3.30	2.63	3.07	2.52
42	2.30	2.32	−0.02	1.37	1.48	6.29	3.09	1.91	3.41	1.91
43	2.70	2.03	0.67	1.42	0.78	7.10	3.09	1.91	3.41	1.91
44	2.35	2.22	0.13	1.65	0.80	9.01	3.09	2.20	3.41	2.02
45	2.48	2.22	0.26	1.96	1.10	9.01	3.08	2.52	3.43	2.53
46	2.51	2.78	−0.27	−0.07	2.28	8.35	3.05	2.64	3.39	2.54
47	2.15	1.90	0.25	NS	0.80	7.68	3.09	2.32	5.84	1.96
48	1.96	2.02	−0.06	NS	1.10	7.68	3.09	2.43	5.89	2.57
49*	2.51	2.04	0.48	NS	1.90	5.88	2.72	2.95	3.92	3.85

[a] Compounds not included in the regression analysis have asterisks. [b] When the denominator of the sweet/bitter ratio (ref 2) is 0, the taste quality is expressed qualitatively as not sweet (NS). [c] Abbreviations used: T, tasteless; I, insoluble; NI, not isolated.

Table II. Development of Equation 1

constant	log P	L	W_l	W_u	r	s
0.99	0.71				0.82	0.42
1.78	0.70		−0.28		0.86	0.39
2.64	0.69		−0.22	−0.34	0.87	0.36
2.80	0.62	0.17	−0.40	−0.64	0.92	0.31

Table III. Squared Correlation Matrix for Variables Used in the Derivation of Equation 1

	log P	L	W_l	W_u	W_r
L	0.02	1.00			
W_l	0.01	0.00	1.00		
W_u	0.02	0.32	0.05	1.00	
W_r	0.00	0.00	0.05	0.06	1.00
W_d	0.00	0.04	0.02	0.09	0.30

II shows the development of eq 1 and Table III the degree of independence of these variables and those used in eq 1.

Among the compounds whose taste intensity was reported, eight compounds, **3**, **5**, **12**, **13**, **17**, **29**, **34**, and **49** (Chart I), were excluded from the correlation, but their taste potency was calculated by eq 1. The epoxide moiety of compound **3** can not be constructed by the present program but was approximated by the accessible cyclopropane ring. Similarly, the strained, bicyclo structure of compound **49** was constructed by normal sp^2 and sp^3 carbons. The deviations of the calculated values from the observed ones for these two compounds are 0.36 and 0.48, respectively, which appear to be permissible as such, supporting the approximation. The log P of compound **5**, i.e., π of the methylated oxime moiety, is presently hard to estimate because of the lack of appropriate data. Compound **17** has the glycol moiety which may raise the

taste potency, as glycols tend to show a sweet taste.[1] A positively larger Δlog A value for compound **13** than compound **12** appears to indicate that the carboxylate anion is working as another factor to raise the taste potency more than the free carboxylic acid species, possibly an electrostatic interaction with the receptor at the position where these two groups locate. The observed values for the taste potency of compounds **29** and **34** fit well with the calculated ones (Table I). Thus, the extra methyl at the basic oxime end appears to reduce the sweetness but not the potency. The compounds reported to be insoluble (**19**), not isolable (**36**), and tasteless (**18**) were also excluded from the analyses. The calculated value for compound **18** suggests a significant taste potency, despite the fact that it is reported to be tasteless,[2] and the reason for this discrepancy remains uncertain.

The fact that eq 1 correlates the activity excellently in terms of the taste potency, which includes both the sweet and bitter tastes, suggests that the sweetness and bitterness receptors have common features.

Structural Discrimination of Sweet and Bitter Tastes. Acton et al.[2] listed the ratios of the sweet to bitter tastes of perillartines. Attempts to correlate the ratio quantitatively with the variations in structure were, however, not successful.

In Table I, the sweetness of the compounds is expressed by log (sweet/bitter), and the compounds with log (sweet/bitter) > 0.0 (the sweet/bitter ratio > 1.00) are taken as sweet. Qualitatively, the fact that compounds **28**, **37**, **47**, and **48** with larger W_r values than 5.8 are bitter compounds suggests that the length in the W_r direction disfavors the sweetness. Similarly, compounds **12–17**, **20**, and **21** with larger W_u values than 3.5 and compounds **12**, **13**, **21**, **27**, **32**, and **33** with larger W_l values than 3.5 are not sweet. Some of these compounds have more than one detrimental steric factor to sweetness, i.e., compounds **12**, **13**, **20**, and **21**. Exception from these criteria is compound **9** whose sweetness is −0.10 by the logarithmic term (the sweet/bitter ratio = 16/20). This compound is considered to be a borderline case between sweet and bitter species. Incidentally, the original authors[2] have assorted this compound into the sweet family. The bitter compounds **23–26** with little conspicuousness in the steric factors possess heteroatoms in the ring at the 4 or 5 position. Compound **22** also has oxygen at position 3, but this compound is rather sweet or at least less bitter. Thus, some position-specific effect is considered to be operative to deprive of the sweetness, presumably an electronic interaction with the acidic surface of the receptor.

Nitro- and Cyanoanilines. Deutsch and Hansch[4] have analyzed the relative sweetness (RS) of nine substituted nitroanilines, resulting in the following equation as the best correlation: log RS = $1.610\pi - 1.831\sigma + 1.729$ ($r = 0.936$; $s = 0.282$), where the σ value of the 2 substituent is directed to the nitro group at the 5 position. More recently, the equation was improved by replacing the electronic term with σ^+.[5] From these equations, they suggested the high dependency of relative sweetness on hydrophobic bonding and basicity of the compound, although the activity data used by these authors is a ratio of weights of sucrose and of the compound tested which gave the same intensity.

Using 14 nitroanilines (**50–64**; Chart II),[10,11] including four compounds (**56**, **57**, **61**, and **62**) which have not been included in the previous analyses,[4,5] and six cyanoanilines,[11] the effect of the various independent variables was examined by regression analysis. The sweet intensity expressed by log A (Table IV) for these series of compounds is the logarithm of the molar sweetening potency calculated from the original weight ratio. The activity of four compounds, **57–60**, has been determined by Verkade et al.[11] and Blanksma et al.[10] Since the correspondence between the data from these laboratories was very good, the simple correlation coefficient being 1.00 with a slope of ca. 1.0, three compounds, **61–63**, reported by Verkade et al.[11] were further incorporated into the analyses.

Chart II

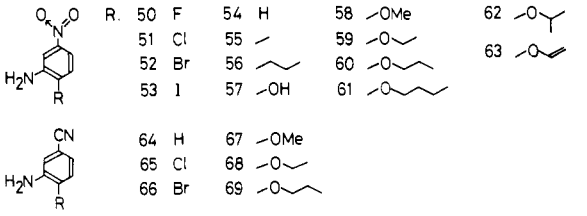

Table IV. Relative Sweetness and Physicochemical Parameters of Aniline Derivatives

	log A				
no.	obsd	calcd by eq 4	Δlog A	L	W_l
50	1.26	1.63	−0.37	6.87	4.15
51	2.31	2.14	0.17	7.74	4.11
52	2.71	2.21	0.50	8.04	4.18
53	2.98	2.53	0.45	8.45	4.10
54	1.21	1.32	−0.11	6.28	4.15
55	2.17	1.75	0.42	7.09	4.15
56	3.02	3.11	−0.09	9.14	4.94
57	1.96	1.68	0.28	6.96	4.15
58	2.21	2.39	−0.18	8.20	4.11
59	2.87	2.84	0.03	9.02	4.09
60	3.46	3.12	0.34	10.27	4.37
61	2.79	2.98	−0.19	11.08	4.78
62	2.54	2.84	−0.30	9.02	4.09
63	3.06	3.15	−0.09	10.44	4.41
64	0.94	1.32	−0.38	6.28	4.15
65	2.13	2.14	−0.01	7.74	4.11
66	2.46	2.21	0.25	8.04	4.18
67	1.89	2.39	−0.50	8.20	4.11
68	2.63	2.84	−0.21	9.02	4.09
69	3.11	3.12	−0.01	10.27	4.37

Among the equations with various combinations of parameters defined under Methods, eq 2 for nitroanilines and eq 3 for cyanoanilines were the best correlations. These

$$\log A = 0.50L(\pm 0.17) - 1.42W_l(\pm 1.22) + 4.17(\pm 4.37) \quad (2)$$

$$n = 14,\ r = 0.90,\ s = 0.32$$

$$\log A = 0.53L(\pm 0.27) - 2.14(\pm 2.24) \quad (3)$$

$$n = 6,\ r = 0.94,\ s = 0.29$$

results indicate that the longer 2 substituents favor the sweetness through both series of compounds. The insignificance of W_l in eq 3 is due to a narrow range of variation in the structure of the cyanoaniline derivatives in this direction. Since the coefficients of the L term in eq 2 and 3 overlap within the 95% confidence interval, these two sets of compounds were combined to give eq 4. The

$$\log A = 0.52L(\pm 0.14) - 1.37W_l(\pm 1.08) + 3.71(\pm 3.49) \quad (4)$$

$$n = 20,\ r = 0.90,\ s = 0.32$$

additions of log P and σ or σ^+ terms singly or in combination did not give significant results.

The direction to which the 2 substituents extend is assumed in this study as the same side as the amino group (Figure 1). Even if they are directed to the opposite side,

however, the results are not altered significantly in terms of the steric dimensions. In other words, an ambiguity exists as to the real location of the amino group on the receptor surface. The collinearity between L and W_l is not significant, the squared simple correlation coefficient being 0.36.

Discussion

The negative coefficient of the W_u term in eq 1 for perillartines means that the more planar the molecule, the higher the taste potency. Although the W_d term did not enter into the correlation because of the poor variations of the compounds investigated, the thickness in the W_d direction would disfavor the taste potency. The widths in the W_l and W_u directions depress the taste intensity as well as the sweetness. Despite the fact that the W_r value varies significantly, it does not affect the taste potency so far as eq 1 is concerned but does affect the taste quality. Accordingly, there appears to exist some sort of interaction in the W_u and W_l directions, which are responsible for both the binding and taste characteristics. The interaction at the region directed to the W_r direction does not seem to be responsible for the binding, as the addition of the W_r term to eq 1 does not improve the correlation. These considerations appear to suggest that the taste sensory triggering is caused by a conformational modification of the receptor. The basicity at the C_4–C_5 region of the heterocyclic perillartine derivatives (**23**–**26**) is also considered to be responsible for the conformational change of the receptor leading to the bitter taste. In summation, Figure 2 has been drawn to show schematically these considerations on binding of the perillartines to the receptor. In Figure 2A, the maximal contour viewed from the C_1 atom to the L direction of the sweet perillartine molecules is overlapped with those of the bitter analogues. Figure 2B is the view from the upside. The two compounds, **29** and **34**, which possess an extra methyl at the oxime carbon are reportedly bitter compounds,[2] with sweet/bitter ratios of 0/66 and 0/75, respectively. Thus, there may exist an additional interaction site on the receptor surface in the vicinity of the basic end.

The positive coefficient of the log P term in eq 1 may reflect the fact that perillartines exert their effect by a single aqueous–lipid partitioning, i.e., partitioning from saliva onto the receptor site of the tongue. The relative sweetness of nine nitroanilines (**50**–**58**) has been previously shown to be linearly related to the hydrophobic and electronic properties of the molecule by regression analysis.[4,5] With 21 compounds (**50**–**69**), the present results provide somewhat different features, such that the steric factors predominate in determining the sweet potency. The log P was insignificant in eq 2–4. This result appears to indicate a somewhat different mode of interaction between the two classes of compounds, although the possibility remains that the hydrophobic and electronic parameters may be incorporated into eq 2–4 with the compounds of more diverse variations in structure.

The present method of determining the steric dimensions of aniline derivatives is based on the assumption that the oxime moiety in perillartines and the nitro or cyano group in anilines are the common basic end because of the overall similarity of the structure between both classes. Alternatively, it is also possible that the amino group is the basic part of the class. Because the steric parameters are linearly related between nitrobenzene and aniline references, i.e., the L in the former is linearly related to W_l in the latter and the W_u is the same etc., the quantitative analyses like eq 2–4 are of little value for solving this problem. In the case of the aniline reference, however, the steric dimensions disfavor the sweet taste as well as the taste potency according to the receptor map drawn for the perillartine derivatives, if one assumes the identical receptor. Due to the bulky substituents ortho to the amino group, the compounds become to possess large W_l values. This conflicts with the reported sweet potency of the aniline derivatives. At any rate, the present results show that the steric dimensions of the compounds are commonly important through both series in determining the taste potency.

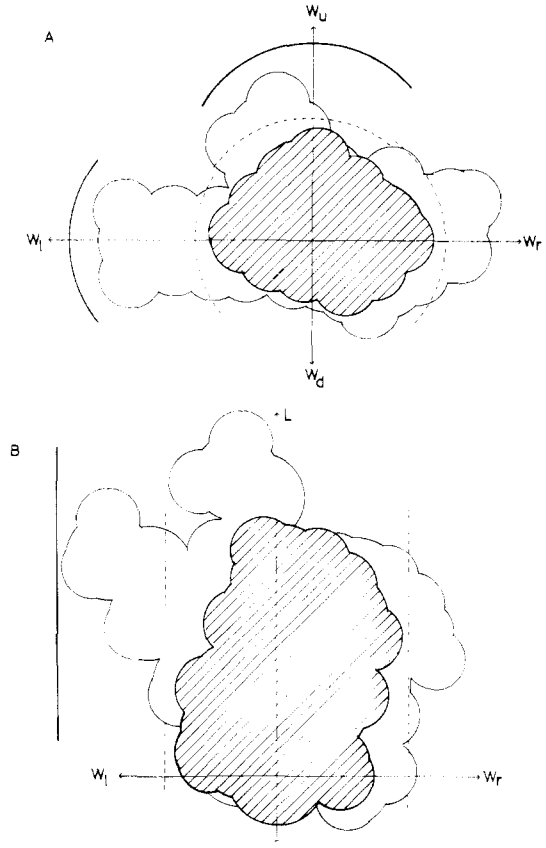

Figure 2. Perillartines–receptor binding model. The maximum contour of the sweet perillartine derivatives is striped. Unfigured is that of the bitter analogues. Solid lines represent the spatial walls for taste potency, and dashed lines the bitter barriers. (A) The view from the C_1 atom to the L direction. (B) The view from the upside.

Within the congeneric perillartine derivatives, it has been shown that the taste potency, i.e., both sweet and bitter intensities, vs. structures can be formulated in one equation in terms of common physicochemical parameters. Although the sweet/bitter ratio can not be analyzed quantitatively by regression analysis, it has been shown that predominantly the position-specific steric factors participate in the discrimination of sweet and bitter tastes. These results will be of value for designing sweetners of better quality. On the other hand, the comparative QSAR studies of perillartines and aniline derivatives are not sufficient to transpose information gained in one class to another. However, they would be extended with future studies on other diverse classes of compounds.

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