Structure–Activity Studies on Sulfamate Sweetners III: Structure–Taste Relationships for Heterosulfamates

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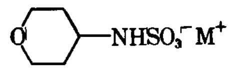
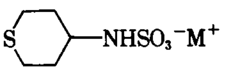
Abstract ☐ Eleven heterosulfamates have been synthesized, characterized, and evaluated for sweetness. Measurements of the molecular dimensions (x, y, z, and V) of these sulfamates and 22 others that had been reported previously and evaluated for sweetness have been made using Corey–Pauling–Koltun space-filling models. The first-order molecular connectivities (${}^1\chi^v$) of all the heterosulfamates have been calculated. The statistical technique of linear discriminant analysis was applied to the complete set of 33 compounds and to a reduced set of 27 compounds. The analysis was performed using the above five variables (x, y, z, V, and ${}^1\chi^v$) and various subsets thereof. For the complete set of compounds, seven variable subsets were identified which yielded correct classifications of 27 and 28 compounds. A similar analysis of the reduced set did not improve the misclassification rate.

Keyphrases ☐ Heterosulfamates—synthesis, classification by linear discriminant analysis, structure–taste relationship ☐ Sweetners, sulfamate—structure–taste relationship, classification by linear discriminant analysis ☐ Linear discriminant analysis—classification of heterosulfamates, molecular connectivity correlations

Previous studies (1–4) on heterosulfamates have shown that when one of the ring carbons of cyclohexylsulfamate is replaced by an oxygen or nitrogen atom, sweetness is lost, whereas replacement by a moiety containing a sulfur atom results in the retention of sweetness. Compounds X (1), XVIII (2), and XX (1) are nonsweet while IX (2), XI (3), and IV (4) are sweet.


X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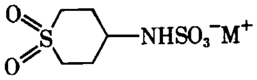
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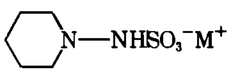
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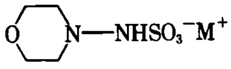
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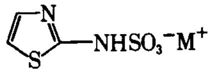
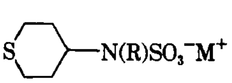
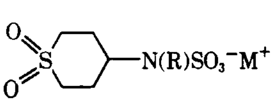

IV

Furthermore, one of the basic structure–taste rules found for carbosulfamates does not appear to apply to heterosulfamates, namely, that the presence of a free hydrogen on the nitrogen of the sulfamate function was essential for sweetness (5). This was shown by the taste evaluation of the series of cyclic sulfides (IX, XXIV, XXI, and XXV) and sulfones (XI, XXIII, and XXII) which are sweet (3).


IX: R = H
XXIV: R = $—CH_2CH_3$
XXI: R = $—(CH_2)_3CH_3$
XXV: R = $—CH_2CH_2OH$


XI: R = H
XXIII: R = $—CH_2CH_3$
XXII: R = $—(CH_2)_3CH_3$

Since only a few other heterosulfamates have been reported, 11 new heterosulfamates (both cyclic and open-chain) were synthesized and several structure–taste relationships were established from measurements of the molecular dimensions and molecular connectivities of these and other heterosulfamates reported previously.

EXPERIMENTAL

Synthesis—All sulfamates except VII and XII were synthesized by previously described methods (5, 6).

5-Methylisoxazolo-3-sulfamate (VII)—A solution of 3-amino-5-methylisoxazole (5 g, 0.05 mole) in dry nitrobenzene (40 ml) was cooled to 0°. Chlorosulfonic acid (4.5 g, 0.05 mole) was added with stirring at a rate such that the temperature did not rise above 5°. The mixture was stirred at room temperature for 3 hr. Ether (20 ml) was added and the orange solid that precipitated from the solution was removed by filtration, dissolved in 0.05 *M* sodium hydroxide (20 ml), and the solution was extracted with ether (2 × 20 ml). On removal of the ether under reduced pressure, an oily residue remained. On chilling this gave rise to a white solid which was the amine salt of the required sulfamate. Attempts to prepare this compound by the method of Hurd and Kharasch (4) failed. By employing the dipolar aprotic solvent nitrobenzene, a small yield (2.4%) was obtained. Possibly in this solvent protonation of the ring nitrogen of the isoxazole and consequent reduced basicity of the amino group is inhibited. The basicity of the oxazole was such that the sulfamate formed was the oxazole salt rather than the sodium salt.

3-Thia-3,3-dioxocyclopentylsulfamate (XII)—A solution of 3-thia-3,3-dioxocyclopentylamine (5 g, 0.037 mole) in ethanol (40 ml) was cooled to ~0°. Chlorosulfonic acid (3.52 g, 0.03 mole) was added in a dropwise manner with stirring. The mixture was stirred at room temperature for 3 hr, and then ethanol was removed under reduced pressure. The resulting yellow solid was dissolved in 2 *M* sodium hydroxide, and the liberated amine was extracted with ether (3 × 25 ml). The aqueous layer was then concentrated to ~10 ml and the precipitated amine salt of the sulfamate was removed by filtration and then recrystallized from 95% ethanol. Again the amine was sufficiently basic to form this salt rather than the expected sodium salt. The yields of the sulfamates synthesized were 2–20%.

Analysis and Characterization—The sulfamates prepared gave satisfactory (within ±0.5%) C, H, and N analyses except for I, II, VII, XXVI, and XXVII. Analytical data (C, H, and N) for all new compounds are given in Table I. It should be noted that occluded solvent of recrystallization is a common problem with sulfamates (5, 7, 8). Despite repeated recrystallization, the elemental analysis for I could not be improved; however, this compound displayed the sulfamate properties described below.

IR spectra of all the sulfamates prepared were recorded[1]. The sulfamates gave the following characteristic bands (9): 3400–3190 (NH), 1240–1210 (asymSO_3), 1203–1170 (symSO_3), 1072–1040 (symSO_3), and 730–660 cm^{-1} (NS). All the prepared sulfamates gave a positive "sulfamate" test (2).

Taste Analysis —Analysis was carried out as previously described (10). Two of the sulfamates (VII and XII) were isolated and purified as their amine salts ($RHNSO_3^-NH_3^+R$) and were tasted as such, since it is known that the salt-forming group does not influence the taste of sulfamates (5, 11).

Measurements with Models and Molecular Connectivity Measurements—The measurements with the Corey–Pauling–Koltun models were carried out as previously described (10), and the parameters x, y,

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[1] Perkin-Elmer 337 spectrophotometer using Nujol mulls.

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Table I—Analytical Data for New Sulfamates

Compound	Found, % C	Found, % H	Found, % N	Formula	Required, % C	Required, % H	Required, % N
I	19.38	4.12	6.89	$C_5H_{10}NSO_4Na{\cdot}3H_2O$	23.42	6.22	5.44
II	29.22	3.02	7.11	$C_5H_6NSO_4Na$	30.15	3.02	7.03
III	28.21	11.13	5.14	$C_6H_{13}N_2SO_3Na{\cdot}2H_2O$	27.69	10.76	5.00
VII	35.32	5.97	19.8	$C_8H_{12}N_4SO_5$[a]	34.8	4.4	20.3
XII	27.38	5.44	7.82	$C_8H_{18}N_2S_3O_7$[a]	27.42	5.14	8.00
XIII	36.52	6.63	12.27	$C_7H_{15}N_2SO_3Na$	36.52	6.52	12.27
XIV	49.13	5.83	9.80	$C_{12}H_{17}N_2SO_3Na$	49.32	5.82	9.59
XV	34.38	6.23	11.51	$C_7H_{15}N_2SO_4Na$	34.14	6.23	11.38
XIX	30.66	6.47	12.03	$C_6H_{13}N_2SO_3Na{\cdot}1H_2O$	30.76	6.41	11.96
XXVI	28.22	5.49	5.75	$C_5H_{12}NSO_4Na{\cdot}\frac{1}{2}H_2O$	28.00	6.09	6.54
XXVII	24.98	5.44	11.75	$C_5H_{13}N_2SO_3Na{\cdot}2H_2O$	25.00	7.08	11.66

[a] Isolated as the amine salt of the sulfamate.

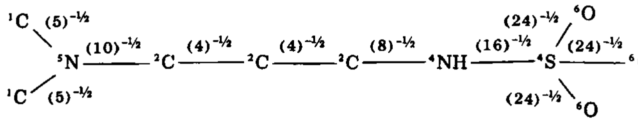
z, and V (*i.e.*, $x{\cdot}y{\cdot}z$) were determined as before (Table II). The values for the molecular connectivity (χ) for the different sulfamates were determined by considering the valence electrons, whether bonded or nonbonded. The δ values are considered to be the difference between the number of valence electrons z^v and the number of hydrogen atoms h_i:

$$\delta_i^v = z^v - h_i \qquad \text{(Eq. 1)}$$

Thus, applying this to oxygen in an alcohol $\delta^v = z^v - h_i = 6 - 1 = 5$. The δ^v values for heteroatoms are given in Table III (12). δ^v can be used to calculate a valence chi-term of the first order (${}^1\chi^v$) by the expression:

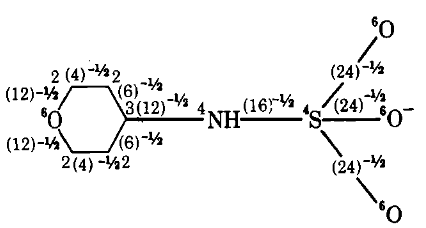
$${}^1\chi^v = \Sigma(\delta_i^v\delta_j^v)^{-1/2} \qquad \text{(Eq. 2)}$$

For example, the chi-term (of the first order) for the sulfamate anion XXVII was calculated as follows:



2 × 0.447
0.316
2 × 0.500
0.354
0.250
3 × 0.204
${}^1\chi^v = 3.43$

When cyclic compounds are considered, a ring correction factor must be used because of the presence of an additional edge (bond). This is accommodated for by the use of 0.5 as a modifying term to be subtracted from ${}^1\chi^v$. For example, the chi-term for the 4-oxacyclohexylsulfamate (χ) was calculated as follows:



2 × 0.289
2 × 0.500
2 × 0.408
0.289
0.250
3 × 0.204
3.545
Correction factor − 0.5
${}^1\chi^v$ 3.05

THEORETICAL

The technique used to facilitate determination of structure–taste relationships is that of linear discriminant analysis. This method is applied when M($\geq$1) measurements (variables) are available for each member of two clearly defined groups and yields a linear function of the variables which best separates the two groups.

The theory of the linear discriminant function is described in many statistical tests (17, 18). Conceptually the method is identical for all values of M (the number of variables observed for each member of each group), but the essential ideas are most easily expanded for the case M = 2. In this case, we have two measurements, say X and Y, for each member of each group. Each member can therefore be represented as a point in the X,Y plane. The linear discriminant function in this case is the line that, in a certain sense, best separates the two groups. If the equation of this line is:

$$aX + bY = k \qquad \text{(Eq. 3)}$$

then mathematically the problem is to use the given (X,Y) data to estimate constants a, b, and k such that the line given by (Eq. 3) separates the two groups in some optimal sense. The extension to the case of M > 2 variables is mathematically straightforward, but conceptually more difficult. We now seek a linear combination:

$$l(X_1,X_2,\dots X_M) = a_1X_1 + a_2X_2 + \dots + a_MX_M = a^1X \qquad \text{(Eq. 4)}$$

where $a^1 = (a_1, a_2, \dots a_n)$ and $X^1 = (X_1, \dots X_M)$ such that an equation of the form:

$$l(X) = k \qquad \text{(Eq. 5)}$$

optimally separates the two groups. In the case M = 3, this is equivalent to finding the plane that best separates the two groups in the three-dimensional space in which they can be represented. For M > 3, we obtain a hyper-plane separating the two groups. Although the geometrical representation breaks down for the case M > 3, the mathematical method is straightforward.

Most statistical packages used on computers will perform this analysis. The package BMDP (19) was used in this case, and it yields the constants a_1, a_2, ... a_M of Eq. 4. The constant k is then chosen to optimize the discriminatory power of the discriminant function $l(X)$. The criterion of optimality usually used involves stochastic assumptions concerning the multivariate normal distribution of the underlying data. Given the nature of this particular data set, the more *ad hoc* criterion of minimizing the number of misclassifications using the discriminant function $l(X)$ has been adopted in this paper.

Suppose one has two groups of compounds and has recorded the values of each of M variables for n_1 members of group 1 and n_2 members of group 2.

Let X_{ijk} $\{i = 1,2; j = 1,2 \dots n_i; k = 1,2 \dots \mathrm{M}\}$ be the value of the k^{th} variable for the j^{th} member of the i^{th} group. Let:

$$\bar{X}_{ik} = \sum_j X_{ijk}/n_i \qquad \begin{matrix} i = 1,2 \\ k = 1,2,\dots \mathrm{M} \end{matrix} \qquad \text{(Eq. 6)}$$

and define the mean vectors of the two groups to be, respectively:

$$\bar{X}_1^1 = (\bar{X}_{11}, \bar{X}_{12}, \dots \bar{X}_{1M}) \qquad \text{(Eq. 7)}$$

$$\bar{X}_2^1 = (\bar{X}_{21}, \bar{X}_{22}, \dots \bar{X}_{2M}) \qquad \text{(Eq. 8)}$$

Further let:

$$S_{kl} = \frac{\sum_i \sum_j (X_{ijk} - \bar{X}_{ik})(X_{ijl} - \bar{X}_{il})}{n_1 + n_2 - 2} \qquad \text{(Eq. 9)}$$

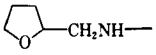
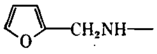
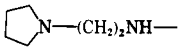
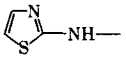
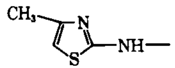
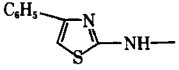
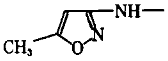
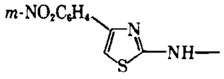
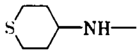
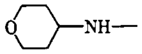
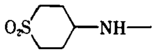
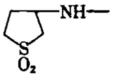
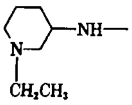
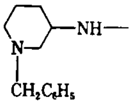
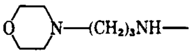
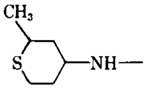
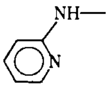
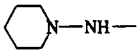
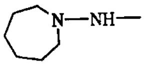
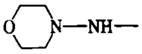
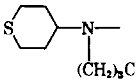
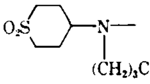
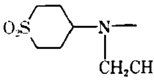
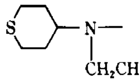
so that:

$$S = (S_{kl}) \qquad \text{(Eq. 10)}$$

is the M × M pooled estimate of the (assumed) common covariance matrix. Then the elements of the vector a of Eq. 4 are given by:

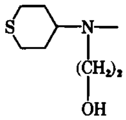
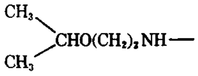
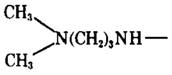
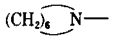
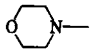
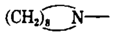
$$a = (\bar{X}_1 - \bar{X}_2)^1 \cdot S^{-1} \qquad \text{(Eq. 11)}$$

Table II—Spatial Parameters for R Groups, Chi-Values, and Taste of Heterosulfamates (R—SO$_3^-$M$^+$)

Compound	R[a]	Name of Sulfamate[b]	Taste[c]	x	y	z	V	$^1\chi^{vd}$	Reference
I		2-Tetrahydrofurfuryl-	N	7.40	4.99	5.92	219.0	3.06	—[e]
II		2-Furfuryl-	N	5.96	4.89	5.72	167.0	2.47	—
III		N-pyrrolidino-2-ethyl-	N	9.64	4.85	5.92	277.0	3.66	—
IV		2-Thiazolyl-	S	7.08	3.66	5.84	151.0	1.97	4
V		4-Methyl-2-thiazolyl-	S	7.08	3.80	6.96	187.0	2.39	4
VI		4-Phenyl-2-thiazolyl-	N	7.08	7.20	8.56	436.0	4.05	4
VII		5-Methylisoxazolo-3-	N	7.80	3.88	5.44	165.0	2.30	—
VIII		4-m-Nitrophenyl-2-thiazolyl-	N	7.08	8.48	9.24	555.0	4.50	4
IX		4-Thiacyclohexyl-	S	5.80	5.44	6.80	215.0	3.18	1
X		4-Oxacyclohexyl-	N	5.52	5.36	6.40	189.0	3.05	1
XI		4-Thia-4,4-dioxocyclohexyl-	S	7.72	5.64	6.56	286.0	3.58	3
XII		3-Thia-3,3-dioxocyclopentyl-	B	6.00	5.64	6.56	222.0	2.99	—
XIII		1-Ethylpiperidinyl-3-	N	6.08	5.68	8.24	285.0	4.12	—
XIV		1-Benzylpiperidinyl-3-	N	11.50	6.80	6.32	494.0	5.68	—
XV		N-n-Propylmorpholino-	N	9.88	5.28	6.40	334.0	4.24	—
XVI		3-Methyl-4-thiacyclohexyl-	S	6.20	5.33	7.88	259.0	3.60	13
XVII		Pyridyl-2-	N	7.72	3.76	6.40	186.0	2.38	4
XVIII		Piperidino-1-	N	7.00	5.30	6.50	241.0	3.22	2
XIX		Azacycloheptyl-	N	7.16	5.04	7.20	260.0	3.72	—
XX		Morpholino-4-	N	5.68	5.36	6.24	190.0	2.80	2
XXI		N-n-butyl-4-thiacyclohexyl-	S	12.72	5.20	6.60	437.0	5.14	3
XXII		N-n-butyl-4-thia-4,4-dioxocyclohexyl-	S	13.56	6.24	6.52	552.0	5.55	3
XXIII		N-ethyl-4-thia-4,4-dioxocyclohexyl-	S	10.56	5.92	6.32	395.0	4.55	3
XXIV		N-ethyl-4-thiacyclohexyl-	S	9.84	5.44	6.40	343.0	4.14	3

continued

Table II—*Continued*

Compound	R[a]	Name of Sulfamate[b]	Taste[c]	x	y	z	V	$^1\chi^{v\,d}$	Reference
XXV		*N*-(2-hydroxyethyl)-4-thiacyclohexyl-	S	11.24	5.28	6.80	404.0	4.24	3
XXVI		3-Isopropoxyethyl-	N	7.64	5.05	6.32	244.0	3.40	—
XXVII		3-Dimethylamino-1-propyl-	B	8.52	4.80	6.12	250.0	3.43	—
XXVIII		Piperidino-1-	N	5.38	5.30	6.40	182	3.49	14, 15
XXIX		Azacycloheptyl-	N	6.44	5.04	7.20	234	3.47	16
XXX		Morpholino-4-	N	4.48	4.48	6.32	127	2.59	15
XXXI		Pyrrolo-1-	N	4.88	4.32	6.00	126	2.47	14, 16
XXXII		Azacyclooctyl-	N	6.48	5.12	7.76	257	3.97	16
XXXIII		Azacyclononyl-	N	6.05	5.20	8.40	264	4.47	16

[a] Measurements were made on the structures indicated. [b] Compounds XXVIII–XXXIII are sulfonates, but may be regarded as secondary sulfamates and are thus included. [c] Key: (S) sweet; (N) nonsweet; (B) bitter. [d] Molecular connectivities were calculated for the total sulfamate anion, *i.e.*, the —SO_3^- moiety was included in the calculations (see *Experimental*). [e] — Values obtained from this work.

and the classification rule is:

classify as group 1 if $a^1X > k$
classify as group 2 if $a^1X \leq k$

The choice of k is then made to minimize the number misclassified by this rule.

RESULTS AND DISCUSSION

In a previous paper, measurements using Corey–Pauling–Koltun (CPK) space-filling models were carried out on carbosulfamates and a semiquantitative structure–taste relationship was established (10). The approach was similar here and measurements of length (x), height (y), and width (z) of R—NH (or R—NR^1) in R—$NHSO_3^-$ (R—$NR^1SO_3^-$) were made using CPK models. V (in Å^3) may be thought of as a measure of the size or three-dimensional structure of R—NH(R—NR^1) and was calculated as previously described. In addition, a molecular connectivity term ($^1\chi^v$) has been calculated (see *Experimental*). The values of x, y, z, V, and $^1\chi^v$ as well as the test data are given for all the heterosulfamates in Table II.

The mathematical analysis has been performed twice: with the complete set of 33 compounds and with a reduced set of 27 compounds (omitting the last six compounds of Table II). Since six compounds of Table II are sulfonates that could be regarded as secondary sulfamates, the analysis has been tried with and without these compounds. As the analysis involving the reduced set did not improve the misclassification rate, it is not described further.

The linear discriminant analysis could be performed using any subset of the five variables. There are 31 such subsets and, to save computation time, a preliminary analysis using a statistically equivalent technique, stepwise logistic analysis (19), enabled identification of the 14 subsets most likely to provide effective discrimination. The discriminant analysis was then performed using these subsets. For the complete set (33 compounds), the most effective variable subset of each (2, 3, 4, 5), the discriminant function a^1X for each of those subsets, the corresponding constant k, and the number of compounds misclassified by the optimal classification rule so derived are given in Table IV.

A discussion of the discriminant analysis applied to the complete data set and using the variable subset (x,$^1\chi^v$) will be utilized to highlight the main points of this type of analysis. From Table IV it can be seen that the dividing line in this case is:

$$-0.63x + 0.58\,^1\chi^v = -3.95 \qquad \text{(Eq. 12)}$$

It can be seen from Table IV that, with the exception of IV, V, IX, XI, XVI, and XXIV, all the sweet compounds lie above and all the nonsweet compounds lie below this line. The mathematically equivalent results for this case are given in Table V, which presents the values of:

$$d = -0.63x + 0.58\,^1\chi^v \qquad \text{(Eq. 13)}$$

for each compound. It can be seen that for all the sweet compounds (with the aforementioned exceptions), $d < k\{-3.95\}$, whereas for all the nonsweet compounds $d > k$.

Detailed results are not presented for the discriminant analyses based on the other variable subsets given in Table IV. From Table IV it can be seen that, although the inclusion of additional variables does not dramatically affect the discriminatory performance, the number of misclassified compounds does decrease (to 5) when one uses the subset x,z,$^1\chi^v$. For this particular case, the discriminant function is:

$$d = -0.86x - 0.81z + 1.31\,^1\chi^v \qquad \text{(Eq. 14)}$$

and the corresponding classification rule is:

classify as sweet if $d < -8.18$
classify as nonsweet if $d > -8.18$

In fact three sweet compounds (IX, XI, and XVI) have values of $d > -8.18$, and two nonsweet compounds (III, XVII) have values of $d < -8.18$. The remaining subsets in Table IV misclassify six compounds in each case. Thus, an accuracy of 85% can be attained for the subset involving the variables x, z, and $^1\chi^v$ with 81% accuracy for all other subsets. For the carbosulfamates an accuracy of >90% could be achieved using the variables x and V only (10). Here the accuracy is not as good but, considering the wide diversity of heterocompounds in Table II, the present correlation can be regarded as reasonable.

A weakness of the x,$^1\chi^v$ subset correlation seems to be that all six misclassified compounds come from the group of 10 sweet compounds, while the 23 nonsweet compounds are classified correctly. One would prefer to see a more even spread of misclassified compounds from the sweet and nonsweet groups as in some of the four or five variable subsets in Table

Table III—Heteroatom Valence Delta-Values

Group	δ^v	Group	δ^v
		—OH	5
—NH	4	—O—	6
		=O	6
$\vert$		O (both nitro)	
—N—	5	O (both carboxylate)	6
=N—(pyridine)	5		
—N=(nitro)	6		
—S—	4		
=S=	4		

Table IV—Discriminant Analysis for Best Subsets

Subset	a^1X	k	Compounds Misclassified		Total Misclassified
			Sweet	Nonsweet	
$x,{}^1\chi^v$	$-0.63x + 0.58{}^1\chi^v$	−3.95	IV, V, IX, XI, XVI, XXIV		6
$y,V,{}^1\chi^v$	$1.62y - 0.02V + 0.65{}^1\chi^v$	+4.21	IX, XI, XVI, XXIII, XXIV	XVII	6
$x,z,{}^1\chi^v$	$-0.86x - 0.81z + 1.31{}^1\chi^v$	−8.18	IX, XI, XVI	III, XVII	5
$x,z,V,{}^1\chi^v$	$-1.01x - 1.08z + 0.01V + 1.06{}^1\chi^v$	−10.50	IX, XI, XVI	III, XV, XVII	6
$x,y,z,{}^1\chi^v$	$-0.81x + 0.34y - 0.88z + 1.01{}^1\chi^v$	−7.49	IX, XI, XVI	III, XV, XVII	6
x,y,z,V	$-0.37x + 1.05y - 0.41z - 0.01V$	−2.37	IV, IX, XI, XVI	XV, XVII	6
$x,y,z,V,{}^1\chi^v$	$-1.06x - 0.08y - 1.12z + 0.01V + 1.08{}^1\chi^v$	−11.17	IX, XI, XVI	III, XV, XVII	6

IV (*e.g.*, the $x,z,{}^1\chi^v$ subset which has three sweet and two nonsweet compounds misclassified).

If one uses the number misclassified and the spread of misclassified compounds between sweet and nonsweet groupings as criteria of significance, then one may concentrate on the last five subsets of Table IV. The importance of spatial or volume effects at the receptor site is clear when one observes that x and either z or y or both are involved in all these subsets. ${}^1\chi^v$ Encodes both volume and electronic effects of bonds (20), and it is noteworthy that this variable occurs in four of these five subsets. With the carbosulfamates, electronic influences were probably small and, hence, a correlation was possible using only spatial parameters. However, with the introduction of various heteroatoms into the sulfamates, electronic effects of bonds could be important, and a more complicated type of correlation would thus be expected.

Molecular connectivity terms have been used in recent years to correlate the sweetness of substituted nitroanilines (21) and the percent sweet/bitter taste of aldoximes, RCH=NOH (22). Thus, ${}^1\chi^v$ was introduced since a correlation with our spatial parameters only was not possible.

In the listing of misclassified compounds, the same compounds appeared: III, IX, XI, XV, XVI, and XVII. It is instructive to look at these more closely in the hope of finding a common factor that may cause their deviation. Compounds IX, XI, and XVI all have a sulfur atom in a six-membered ring in either the disulfide or sulfone form. Compounds IV–VI and VIII also have sulfur atoms in five-membered rings, but these atoms are involved in the aromaticity of the rings. Compound XII has sulfur in a five-membered saturated ring system, and one may regard compounds XXI–XXV as special cases since they all have disubstituted sulfamate nitrogens. It thus seems that the correlations established will consistently misclassify six-membered saturated sulfur ring systems. The reason(s) for the deviation of the three nonsweet compounds III, XV, and XVII are less clear.

Table V—Discriminant Function [a] Values for Subset ($x,{}^1\chi^v$)

Sweet Compounds		Nonsweet Compounds	
Compound	d	Compound	d
IV	−3.31 [b]	I	−2.88
V	−3.06 [b]	II	−2.31
IX	−1.80 [b]	III	−3.94
XI	−2.78 [b]	VI	−2.10
XVI	−1.81 [b]	VII	−3.57
XXI	−5.01	VIII	−1.84
XXII	−5.31	X	−1.70
XXIII	−4.00	XII	−2.04
XXIV	−3.78 [b]	XIII	−1.43
XXXV	−4.61	XIV	−3.93
		XV	−3.75
		XVII	−3.47
		XVIII	−2.53
		XIX	−2.34
		XX	−1.95
		XVI	−2.83
		XVII	−3.37
		XVIII	−1.36
		XXIX	−2.03
		XXX	−1.31
		XXXI	−1.63
		XXXII	−1.77
		XXXIII	−1.21

[a] Discriminant function $d = -0.63x + 0.58\,{}^1\chi^v < -3.95$ sweet, > -3.95 nonsweet.
[b] Misclassified.

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