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Synthesis and taste properties of sodium disubstituted phenylsulfamates. Structure–taste relationships for sweet and bitter/sweet sulfamates

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Forty ring disubstituted phenylsulfamates have been synthesized as their sodium salts. These compounds display a variety of tastes including sweet, bitter and sour. Seven of them gave a predominantly sweet taste, twelve displayed a bitter taste followed by a sweet aftertaste, eleven showed predominant bitterness, five sourness and five gave an aniline- or hydrocarbon-like taste and were not assessed further by the panellists. A plot of z (width of molecule, measured using Corey–Pauling–Koltun (CPK) models) versus first-order molecular connectivity, ${}^1\chi^v$ placed the seven predominantly sweet compounds on the line described by $z = 2{\cdot}27\ {}^1\chi^v - 0{\cdot}158$. Summation of Hammett sigma (σ) values for the X and Y substituents gives $\sum \sigma$, and with these the following structure–taste relationships were derived: Predominant sweetness: $\sum \sigma \geq 0{\cdot}6$, $V_{CPK} \leq 300$ Å^3 and a *meta*-electron with drawing substituent, no *para*-substituent. Bitter/sweet aftertaste: $\sum \sigma \leq 0{\cdot}22$, $V_{CPK} \leq 300$ Å^3.

Some of the starting disubstituted anilines have been reported to be sweet and sulfamation modifies or destroys this sweetness. This is also discussed.

INTRODUCTION

For some years we have been developing structure–sweetness relationships for the sulfamates, RNHSO$_3^-$Na$^+$ (Benson & Spillane, 1976; Spillane & McGlinchey, 1981; Spillane *et al.*, 1983; Spillane & Sheahan, 1989; Spillane *et al.*, 1989). The establishment of these relationships was facilitated by the presence in the literature of reports of synthesized sulfamates, which had been tasted, and thus could be used as starting data bases which we supplemented by further synthesis. Thus, for example, for non-aromatic carbosulfamates, 33 compounds were available and we used these to derive a semi-quantitative SAR and tested this by synthesizing a further 12 compounds (Spillane & McGlinchey, 1981). For heterosulfamates the initial number of compounds which had been synthesized was small (~22); the base was enlarged by synthesizing a further 11 compounds and then an SAR was developed using all 33 compounds (Spillane *et al.*, 1983). For monosubstituted phenylsulfamates only a few compounds had been made (Audrieth & Sveda, 1944) and we added to this very considerably (Spillane *et al.*, 1989). When we began to look at disubstituted phenylsulfamates (**I**) we

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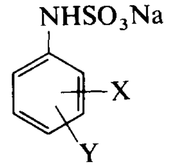

were surprised to find that none had been synthesized *and* tasted. A large-scale synthetic program was therefore embarked upon and, in the present paper, we describe the synthesis and characterization of 40 compounds of structure **I**, the results of their taste analysis and the development of some structure–taste relationships for this group of sulfamates.

MATERIALS AND METHODS

Sodium sulfamates

The following materials were used in the synthesis of the sodium sulfamates: Pyridine (Riedel de Haën, Seelze, Germany), α-picoline (Aldrich, Gillingham, Dorset, UK), chlorosulfonic acid, sodium hydroxide

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and barium chloride (BDH, Poole, UK, general purpose reagents), absolute ethanol, laboratory grade diethyl ether and Whatman (Maidstone, UK) pH indicator paper. Amines needed for the preparation of sulfamates were supplied by Aldrich, Koch-Light Co. (Colnbrook, Bucks, UK) and Fluorochem (Old Glossop, Derbyshire, UK) except the following: 2,4-dimethylaniline, 2,6-dimethylaniline, 3,4-dimethoxyaniline and 3,4-methylenedioxyaniline (Dottikon), 2-methyl, 6-isopropylaniline, 2-ethyl, 6-isopropylaniline and 2-ethyl, 6-sec-butylaniline (Ethyl Corporation) and 2,4-difluoroaniline and 3-chloro, 4-fluoroaniline (Shell Fine Chemicals).

Synthesis

All liquid amines, pyridine, α-picoline and chlorosulfonic acid were dried and distilled before use to ensure that these materials were anhydrous. Solid amines were recrystallized from the appropriate solvents when necessary.

All sulfamates synthesized in this work were obtained by one of the two procedures outlined below.

Procedure I

Chlorosulfonic acid was added dropwise with stirring to excess dry pyridine (10 molar excess) at ≤ 0°C. This was followed by addition of the liquid amine (equimolar with chlorosulfonic acid) or solution of the solid amine in pyridine dropwise with stirring.

The resultant mixture was allowed to come to room temperature and stirred at the same temperature overnight. The solution was basified using 2 M NaOH and the unreacted amine separated by several extractions with diethyl ether. The resultant aqueous solution was concentrated to a low volume to yield the crude product. Repeated recrystallizations from aqueous ethanol gave the pure sulfamate (sodium salt).

Procedure II

Chlorosulfonic acid was added dropwise with stirring to excess dry α-picoline (10 molar excess) at ≤ 0°C. This was followed by the addition of the amine (equimolar with chlorosulfonic acid) as above.

The reaction mixture was heated to 70–80°C in an oil-bath and stirred for 1 h. The heat was then removed and the reaction mixture allowed to come to room temperature. The solution was basified and the work-up was as previously outlined.

Characterization

All compounds synthesized gave a positive and clean (i.e. free of sulfate and chloride ions) sulfamate test (Benson & Spillane, 1976). IR spectra of the sulfamates were recorded as nujol mulls on a Perkin-Elmer 983 G spectrophotometer and the usual characteristic bands observed (Vuagnat & Wagner, 1957; Nofre & Pautet, 1975). Water of recrystallization gave a broad peak at 3500 cm^{-1} accompanied by a sharp peak at 1620 cm^{-1}.

Elemental analyses (C, H, N) were recorded for all sulfamates synthesized. Despite extended periods of drying, it was not possible to remove, in some cases, all the water of recrystallization. C, H, N percentages were within acceptable limits (± 0·5) with the following exceptions:

		C	H	N
2,4-diF.1H_2O	Theory	28·92	2·41	5·62
	Found	29·38	1·66	4·80
2,4-diNO_2.2H_2O	Theory	22·57	2·51	13·17
	Found	21·97	1·51	12·85
2-Me,3-F	Theory	37·00	3·08	6·17
	Found	37·87	2·83	6·17
2-Et,6-Pr^i 1·5H_2O	Theory	45·21	6·51	4·79
	Found	44·94	5·64	4·16

Taste panel procedure

All tasting was carried out at room temperature, 16 ± 0·5°C. Solutions were made up with distilled water and tasted within 24 h. Samples were presented in clean, white plastic cups, not more than five being judged at one session, with water rinses between samples. The sulfamates were assessed by 8 panellists (5 panellists were used where there was insufficient sample).

The four primary standards (Table 1) were tasted at or above their recognition thresholds (Best & Taylor, 1973; Paulus & Reisch, 1980) so that each assessor could detect a definite taste. The panellists were asked to taste samples of the four 'primaries' followed by the sulfamate solution and to choose any of the four primary taste qualities to describe the sulfamate solution being tasted (Table 2). Allowances were made for water of recrystallization in making up sulfamate solutions to the concentrations given.

A sweetness recognition threshold was also determined for 3,5-difluorophenylsulfamate (found to have predominant sweet taste only). Serial dilutions that differed from one another by a factor of 2 were made up in the concentration range 0·006 25–0·000 39 mol/litre. Samples of 8 ml aliquots were presented to the tasters in a randomized (concentration) manner. The threshold level found was 0·000 78 mol/litre (the lowest perceptible taste level recorded by one or more tasters). The mean threshold ± standard deviation is 0·001 03 ± 0·000 42 mol/litre.

Table 1. Concentrations of the four primary taste standards

Taste	Standard	Concentration
Sweet	Sucrose[a]	4·4 × 10^{-2} M (1·5%)
Sour	Citric acid[a]	1·3 × 10^{-4} M (0·01%)
Bitter	Quinine sulphate[a,c]	6·1 × 10^{-6} M (0·0005%)
Salt	Sodium chloride[b]	3·4 × 10^{-2} M (0·2%)

[a] BDH Chemicals.

[b] Riedel de Haën.

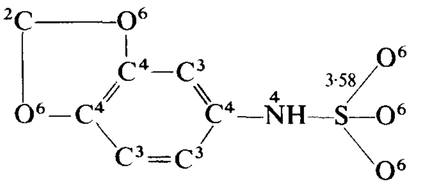
[c] Quinine sulphate had to be stored in the dark as it is light-sensitive.

CPK measurements

Measurements with CPK models were carried out as previously described (Spillane & McGlinchey, 1981). Replicate measurements were at least within 5% (usually better). Measurements were made on the aromatic portion (including the X and Y substituents) only. The values of x, y, z and V_{CPK} are presented in Table 3.

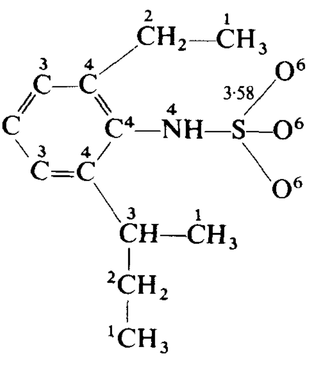
Molecular connectivity calculations

First-order molecular connectivity ($^1\chi^{\mathrm{v}}$) and fourth-order molecular connectivity $^4\chi^{\mathrm{v}}_{\mathrm{pc}}$ were calculated as described by Kier and Hall (1976, 1986). $^4\chi^{\mathrm{v}}_{\mathrm{pc}}$ values did not contribute to our structure–taste relationship and therefore are not presented here. Values of $^1\chi^{\mathrm{v}}$ are presented in Table 3. The following model calculations illustrate the method of computation. A ring correction factor of 0·5 has been used for the methylenedioxy ring compound. This factor is used for saturated ring compounds only.



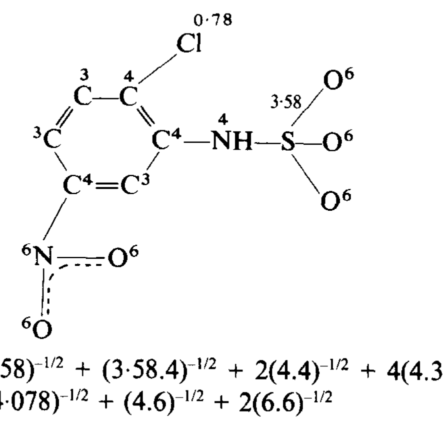
$$^1\chi^{\mathrm{v}} = 3(6.3\cdot 58)^{-1/2} + (3\cdot 58.4)^{-1/2} + 2(4\cdot 4)^{-1/2} + 4(4.3)^{-1/2} + (3.3)^{-1/2} + 2(4.6)^{-1/2} + 2(6.2)^{-1/2} = 3\cdot 884$$

$$^1\chi^{\mathrm{v}} = 3\cdot 884 - 0\cdot 5 = 3\cdot 384$$



$$^1\chi^{\mathrm{v}} = 3(6.3\cdot 58)^{-1/2} + (3\cdot 58.4)^{-1/2} + 3(4.4)^{-1/2} + 3(4.3)^{-1/2} + 2(3\cdot 3)^{-1/2} + (4.2)^{-1/2} + 2(2\cdot 1)^{-1/2} + (3.1)^{-1/2} + (3.2)^{-1/2}$$

$$^1\chi^{\mathrm{v}} = 5\cdot 947$$



$$^1\chi^{\mathrm{v}} = 3(6.3\cdot 58)^{-1/2} + (3\cdot 58.4)^{-1/2} + 2(4.4)^{-1/2} + 4(4.3)^{-1/2} + (3.3)^{-1/2} + (4\cdot 078)^{-1/2} + (4.6)^{-1/2} + 2(6.6)^{-1/2}$$

$$^1\chi^{\mathrm{v}} = 3\cdot 956.$$

RESULTS AND DISCUSSION

In Table 4 the values of the Hammett sigma's (σ s) used for *ortho-*, *meta-* and *para*-substituents in calculating a combined effect (Σ σ) for the influence of X and Y in compounds **I** are given. Table 2 records the taste data for 35 of the 40 compounds synthesized. The remaining five disubstituted sulfamates, i.e. the 2,6-diF, 2,5-diCl, 2-Me,5-Cl, 2-F,5-CF_3 and 2-Br,5-CF_3 all gave an intense aniline- or hydrocarbon-like taste which may have masked other tastes. These five materials could not be assessed further by the tasting panel.

Seven of the compounds in Table 2 gave a predominant sweet taste generally accompanied by strong bitterness or sourness. Twelve displayed a bitter taste followed by a sweet aftertaste. Eleven showed mainly bitterness and five had a predominantly sour component.

Because of our previous successful use of Corey–Pauling–Koltun (CPK) measurements of sulfamates in deriving SARs and because recently V_{CPK} volumes for sulfamates have been shown to give high correlations with both computed van der Waals (V_{W}) and molecular (V_{m}) volumes (Spillane *et al.*, 1992*a*), we commenced our attempts to find structure–taste relationships for the present class of sulfamates by measuring the CPK length (x, Å), width (z, Å) and height (y, Å) of all forty compounds. Measurements were made on the aromatic portion (including the substituents X and Y) only. The —$NHSO_3Na$ side-chain which is present in each compound was not included in the measurements. V_{CPK} (Å^3) was calculated by multiplying x, y and z together. The results of these measurements are recorded in Table 3. Various plots of x, y, z *versus* V_{CPK} were then made, but all showed considerable scatter of the various 'taste types' delineated by the panellists. Due to the strong electronic effects in these aromatic compounds, molecular connectivity of the first order, $^1\chi^{\mathrm{v}}$, which is said to encode both electronic and spatial effects (Kier & Hall, 1981) was also calculated (Table 3) as a potentially useful parameter. A plot of z *versus* $^1\chi^{\mathrm{v}}$ (Fig. 1) gave a reasonable straight line for the seven compounds displaying predominant sweetness. The equation of the line is $z = 2\cdot 27\,^1\chi^{\mathrm{v}} - 0\cdot 158$ (correlation coefficient (r) = 0·967, n = 7, standard error = 0·267, significant at the 0·001 level).

Many of the other 12 compounds having a sweet component in their taste (bitter, followed by sweet aftertaste) are well off the line. However, the plot does appear to bring some order to the problem. A plot of molecular connectivities of the fourth *versus* first order, which established an SAR for sweet aldoximes (Kier, 1980), showed widespread scatter when used for the sulfamates.

A further attempt to quantify the electronic effects in compounds **I** was made by using the Hammett σ_{o}, σ_{m} and σ_{p} constants from Table 4 to calculate the summation of the effects of X and Y. The combined effects are listed as Σ σ in Table 3. The value of Σ σ was obtained for each disubstituted aromatic sulfamate by taking the

Table 2. Percentage of assessors (8) giving the taste quality[a] of sodium disubstituted phenylsulfamates

Sulfamate	Sweet	Sour	Bitter	Salt	Tasteless	Sweet aftertaste
2,3-diF[b]	100·0	0	100·0	0	0	0
2,4-diF	0	75·0	37·5	0	0	0
2,5-diF	100·0	100·0	0	0	0	0
2,6-diF[c]	—	—	—	—	—	—
3,4-diF[b]	0	0	100·0	0	0	0
3,5-diF	100·0	0	12·5	0	0	0
2,3-diCl	12·5	0	100·0	0	0	0
2,4-diCl	0	0	100·0	0	0	0
2,5-diCl[c]	—	—	—	—	—	—
3,4-diCl[b]	0	0	100·0	0	0	60·0
3,5-diCl	50·0	62·5	25·0	0	0	37·5
2,3-diMe	0	25·0	75·0	0	0	87·5
2,4-diMe	0	0	100·0	0	0	62·5
2,5-diMe	12·5	37·5	62·5	0	0	87·5
2,6-diMe	0	0	100·0	0	0	37·5
3,4-diMe	0	12·5	87·5	0	0	75·0
3,5-diMe	25·0	37·5	62·5	0	0	75·0
2,4-diNO_2[b]	0	0	100·0	0	0	0
3,4-diOMe	25·0	37·5	75·0	0	0	62·5
3,4-OCH_2O[b]	0	0	80·0	0	20·0	20·0
3-Cl,4-F	0	0	100·0	0	0	0
2-F,5-Me	0	75·0	25·0	0	0	0
2-Me,5-F	0	50·0	75·0	0	0	12·5
2-Me,3-F	0	37·5	62·5	0	0	50·0
3-Cl,4-Me	0	37·5	62·5	0	12·5	62·5
2-Me,5-Cl[c]	—	—	—	—	—	—
2-F,5-NO_2	87·5	25·0	87·5	0	0	0
2-Me,5-NO_2	100·0	12·5	87·5	0	0	0
2-Cl,5-NO_2[b]	100·0	100·0	0	0	0	0
2-OMe,5-NO_2[b]	0	0	100·0	0	0	0
2-OMe,5-Cl	12·5	37·5	87·5	12·5	0	75·0
2-NO_2,4-OEt	12·5	100·0	0	0	0	0
2-OMe,4-NO_2	12·5	100·0	0	0	0	0
2-F,5-CF_3[c]	—	—	—	—	—	—
2-Cl,5-CF_3	0	37·5	62·5	12·5	0	62·5
2-Br,5-CF_3[c]	—	—	—	—	—	—
2-Me,6-Pr^{i}[b]	0	0	100·0	0	0	60·0
2-Et,6-Pr^{i}[b]	0	0	100·0	0	0	0
2-Et,6-Bu^{s}[b]	0	0	100·0	0	0	0
3-NO_2,4-F[b]	0	0	100·0	0	0	0

[a] All the above compounds were tasted as 0·01 M solutions except the following, which were tasted at the concentrations in parentheses 2-Me,5-NO_2 (0·00106 M), 2-Cl,5-NO_2 (0·00108 M), 2-NO_2,4-OEt (0·0011 M) and 2-OMe,4-NO_2 (0·00112 M).

[b] Five assessors were used to taste these compounds.

[c] These compounds displayed an aniline or hydrocarbon-like taste and therefore were not given to the taste panel.

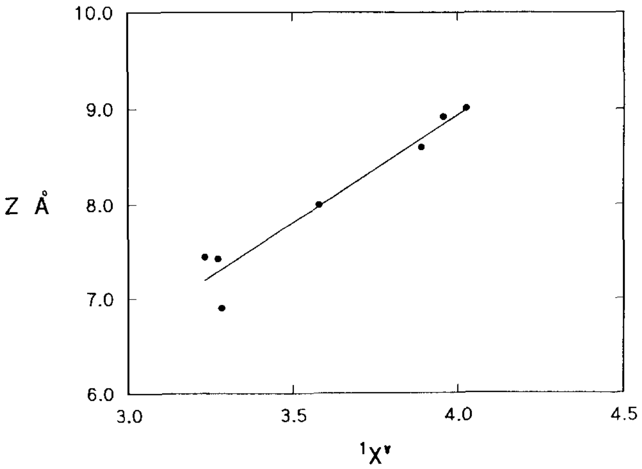


Fig. 1. Plot of z (width of aromatic portion of molecule) *versus* $^1\chi^v$ (molecular connectivity of the first order) for predominant sweet compounds.

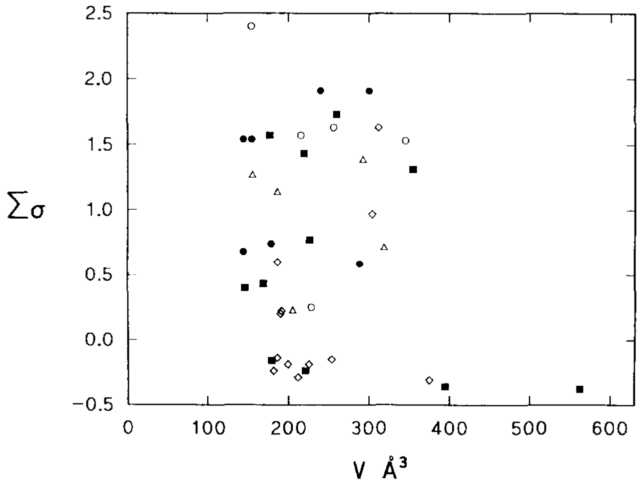


Fig. 2. Plot of $\Sigma\,\sigma$ *versus* V_{CPK} Å^3 for all 40 molecules tasted. ● indicates predominant sweetness; ◇ indicates bitterness followed by sweet aftertaste; ■ indicates bitterness; Δ indicates sourness; ○ indicates aniline- or hydrocarbon-like taste.

Table 3. Molecular connectivity ($^{1}\chi^{v}$), CPK measurements, summation of Hammett Sigma values ($\Sigma\,\sigma$) for X and Y and predominant taste

Sulfamate	$^{1}\chi^{v}$	x(Å)	y(Å)	z(Å)	V_{CPK}(Å^3)^a	$\Sigma\,\sigma$	Predominant taste (>50% of assessors)
2,3-diF	3·283	6·19	3·37	6·90	143·92	1·54	Sweet/Bitter
2,4-diF	3·231	6·73	3·37	6·85	155·43	1·26	Sour
2,5-diF	3·231	6·16	3·37	7·44	154·36	1·54	Sweet/Sour
2,6-diF	3·283	6·18	3·38	7·39	154·13	2·40	Aniline- or hydrocarbon-like
3,4-diF	3·231	6·29	3·37	6·89	145·87	0·40	Bitter
3,5-diF	3·271	5·74	3·38	7·42	144·04	0·68	Sweet
2,3-diCl	4·037	6·69	3·48	7·60	176·64	1·57	Bitter
2,4-diCl	3·985	8·19	3·48	7·70	219·11	1·43	Bitter
2,5-diCl	3·985	6·83	3·48	9·07	215·07	1·57	Aniline- or hydrocarbon-like
3,4-diCl	3·985	7·09	3·46	7·61	186·25	0·60	Bitter with sweet aftertaste
3,5-diCl	4·025	5·69	3·48	9·01	178·29	0·74	Sour/Sweet
2,3-diMe	3·905	6·90	3·93	7·33	199·18	−0·19	Bitter with sweet aftertaste
2,4-diMe	3·899	7·62	3·74	7·42	211·46	−0·29	Bitter with sweet aftertaste
2,5-diMe	3·899	6·90	3·93	8·28	225·03	−0·19	Bitter with sweet aftertaste
2,6-diMe	3·905	6·90	3·80	8·42	220·54	−0·24	Bitter
3,4-diMe	3·899	6·53	3·85	7·22	181·33	−0·24	Bitter with sweet aftertaste
3,5-diMe	3·893	5·66	3·86	8·51	185·79	−0·14	Bitter with sweet aftertaste
2,4-diNO$_2$	3·974	7·13	4·83	7·56	260·53	1·73	Bitter
3,4-diOMe	4·077	7·75	5·79	8·58	253·40	−0·15	Bitter with sweet aftertaste
3,4-OCH$_2$O	3·050	6·92	3·78	6·83	178·90	−0·16	Bitter
3-Cl,4-F	3·608	6·35	3·48	7·64	168·56	0·43	Bitter
2-F,5-Me	3·542	6·17	3·76	8·03	186·16	1·13	Sour
2-Me,5-F	3·542	6·98	3·76	7·79	204·50	0·22	Bitter/Sour
2-Me,3-F	2·927	6·68	3·78	7·56	190·69	0·22	Bitter with sweet aftertaste
3-Cl,4-Me	3·919	6·53	3·81	7·62	189·64	0·20	Bitter with sweet aftertaste
2-Me,5-Cl	3·919	6·83	3·81	8·74	227·45	0·25	Aniline- or hydrocarbon-like
2-F,5-NO$_2$	3·579	6·22	4·83	8·00	240·27	1·91	Sweet/Bitter
2-Me,5-NO$_2$	3·890	6·93	4·83	8·60	288·17	0·59	Sweet/Bitter
2-Cl,5-NO$_2$	3·956	6·98	4·83	8·92	300·67	1·91	Sweet/Sour
2-OMe,5-NO$_2$	4·002	6·79	5·64	9·26	354·15	1·31	Bitter
2-OMe,5-Cl	4·031	6·72	4·84	9·35	303·72	0·97	Bitter with sweet aftertaste
2-NO$_2$,4-OEt	4·590	8·23	5·14	7·53	318·58	0·71	Sour
2-OMe,4-NO$_2$	4·002	8·10	4·40	8·20	292·39	1·38	Sour
2-F,5-CF$_3$	3·670	6·37	4·75	8·46	255·89	1·63	Aniline- or hydrocarbon-like
2-Cl,5-CF$_3$	4·236	7·15	4·62	9·42	311·40	1·63	Bitter with sweet aftertaste
2-Br,5-CF$_3$	4·650	7·49	4·80	9·60	345·05	1·53	Aniline- or hydrocarbon-like
2-Me,6-Pr^{i}	5·426	7·86	4·92	9·70	347·27	−0·31	Bitter with sweet aftertaste
2-Et,6-Pr^{i}	5·987	8·00	4·64	10·62	394·21	−0·36	Bitter
2-Et,6-Bu^{s}	5·947	7·68	6·55	11·18	562·37	−0·38	Bitter
3-NO$_2$,4-F	3·624	6·28	4·79	7·57	227·75	0·77	Bitter

$^a V_{CPK} = x.y.z.$

algebraic sum of the appropriate individual σ values for X and Y from Table 4.

A plot of $\Sigma\,\sigma$ *versus* V_{CPK} (Fig. 2) together with examination of the $\Sigma\,\sigma$ values in Table 3 allows derivation of SARs for the seven predominantly sweet compounds, i.e. 3,5-diF, 2,3-diF, 3,5-diCl, 2,5-diF, 2-F,5-NO$_2$, 2-Cl,5-NO$_2$ and 2-Me,5-NO$_2$ and nine of the 12 compounds showing 'bitterness followed by a sweet aftertaste'.

For predominant sweetness: $\Sigma\,\sigma \geq$ ~0·6, $V_{CPK} \leq$ 300 Å^3 and (at least one) *meta*-electron–withdrawing substituent present, no *para*-substituent.

For bitter/sweet aftertaste: $\Sigma\,\sigma \leq$ 0·22, $V_{CPK} \leq$ 300 Å^3. Three, i.e. 3,4-diCl ($\Sigma\,\sigma$ = 0·6, V_{CPK} = 186), 2-Cl,5-CF$_3$ ($\Sigma\,\sigma$ = 1·63, V_{CPK} = 311) and 2-OMe,5-Cl ($\Sigma\,\sigma$ = 0·97, V_{CPK} = 304), of the 'bitter/sweet aftertaste' group are exceptions.

Using these SARs, the absence of sweetness in the eleven compounds classed as predominantly bitter and the five classed as being predominantly sour can be explained in nearly all cases. The lack of sweetness in eight of the eleven bitter compounds and four of the five sour compounds can be rationalized by reference to the criteria given.

One of the bitter compounds, 2,3-diCl ($\Sigma\,\sigma$ = 1·57, V_{CPK} = 177) should be sweet and two others 2,6-diMe ($\Sigma\,\sigma$ = −0·24, V_{CPK} = 221) and 3,4-OCH$_2$O ($\Sigma\,\sigma$ = −0·16, V_{CPK} = 179) should show a sweet aftertaste. One of the sour compounds, 2-Me, 5-F ($\Sigma\,\sigma$ = 0·22, V_{CPK} = 204), should also give a sweet aftertaste. These four compounds are the only exceptions from the groups of bitter (11 compounds) and sour (5 compounds) disubstituted sulfamates studied.

Eight of the starting disubstituted anilines are reported to be sweet. Thus, compounds **II** (Blanksma & Hoegen, 1946; Blanksma *et al.*, 1946), compounds **III**

Table 4. Hammett sigma values used in the calculations of $\Sigma\ \sigma$

Substituent	σ_0	σ_m	σ_p
F	1·20[a]	0·34[b]	0·06[b]
Cl	1·20[a]	0·37[b]	0·23[b]
Br	1·10[a]		
Me	−0·12[a]	−0·07[b]	−0·17[b]
Et	−0·17[a]		
Pr^i	−0·19[c]		
Bu^s	−0·21[c]		
CF_3		0·43[b]	
NO_2	0·95[d]	0·71[b]	0·78[b]
OMe	0·60[a]	0·12[b]	−0·27[b]
OEt			−0·24[b]
OCH_2O		−0·16[e]	−0·16[e]

[a] Hess *et al.* (1971).

[b] McDaniel and Brown (1958).

[c] These values were estimated from a slight extrapolation of a plot of σ_0 values (Hess et al., 1971) versus Taft's σ^* (Newman, 1956) which had the points for the following substituents on a straight line: F, CO_2H, Cl, Br, OH and Me.

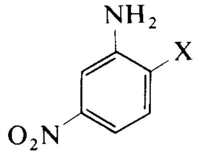
[d] Thompson and Steel (1956).

[e] Hammett (1940).

(Bragg *et al.*, 1978) and compound **IV** (Blanksma *et al.*, 1946) all elicit a sweet taste. In fact, in the case of compounds **II** a QSAR (quantitative structure activity (taste) relationship) has been derived using the compounds shown together with 5 others (Deutsch & Hansch, 1966).

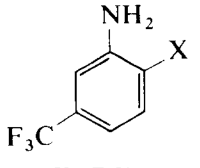
Three of the amines **II** (X = F, Cl, Me) retained sweetness on sulfamation and amine **III** (X = Cl) was bitter with a sweet aftertaste after being sulfamated. Amine **II** (X = OMe) became bitter, amines **III** (X = F, Br) gave a hydrocarbon-like taste and amine **IV** became sour on sulfamation. In an earlier communication we had reported all amines **II** as giving non-sweet sulfamates and that the 3,5-diCl (Spillane & Sheahan, 1991) and 3,5-diF (Spillane *et al.*, 1992*b*) were not sweet. These assessments were made on cursory, preliminary examinations where the faint sweetness of these compounds was missed. The present taste data were obtained after rigorous assessment by the procedures described (see above).

II



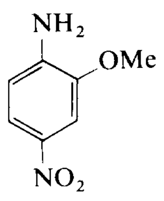
X—F,Cl,Me,OMe

III

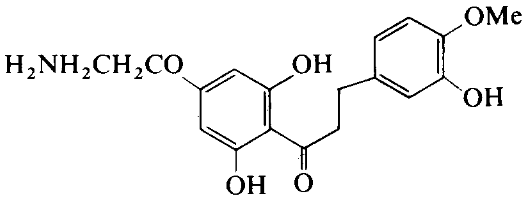


X F,Cl,Br

IV



V



Some years ago (DuBois & Stephenson, 1980) the sweet dihydrochalcone (**V**) was sulfamated and it was found that sweetness was retained on sulfamation.

The sulfamation of the side-chain of this compound probably does not interfere with the Shallenberger AH,B sites, whereas sulfamation of compounds **II**, **III** and **IV**, we suspect, has interfered with the operation of the AH,B mechanism and thus the taste of the molecules may vary on sulfamation.

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