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Synthesis and taste properties of sodium monosubstituted phenylsulfamates

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Thirty-four monosubstituted *ortho*-, *meta*- and *para*-phenylsulfamates have been synthesized, characterized and tasted. The compounds (as sodium salts) display all four primary tastes often in combination.

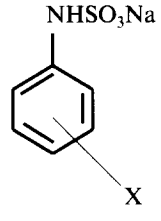
Some structure–sweet taste relationships have been derived using measurements made with CPK models and using Hammett sigma values for the various substituents.

For the 14 *meta*-substituted compounds (including five previously made) those having x (the length of the aromatic portion including the substituent) in the range 5·82 ± 0·12 Å and V_{CPK} (= $x.y.z$) ≤ 295 Å^3 displayed some sweetness, this being much more pronounced and exclusive for those compounds with $V_{CPK} \leq 170$ Å^3. All the sweet *meta*-compounds had σ_m in the range −0·07 to + 0·56. The *ortho*-compounds that showed some sweet component in their taste generally had σ_o in the range −0·30 to + 0·81 and the *para*-compounds nine of which had a sweet aftertaste had σ_p in the range −0·27 to + 0·66.

INTRODUCTION

In the original report of sulfamate sweeteners a number of monosubstituted phenylsulfamates (**I**) were synthesized and none was found to be sweet though it was noted that the parent compound, *N*-phenylsulfamate (**I**, X = H) 'possessed only a sweet aftertaste' (Audrieth & Sveda, 1944). A few sweet thiazole aromatic sulfamates have been reported (Hurd & Kharasch, 1946) and their sweetness has been accounted for in a structure–taste relationship (Spillane *et al.*, 1983). These, however, are more correctly regarded as being heterocyclic compounds rather than simple aromatics and cannot be included among the compounds described by structure **I**.

In a preliminary note re compounds **I** we described the discovery of the sweetness of five *meta*-substituted compounds **I** (X = F, Cl, Br, Me, CN) and carried out relative sweetness (RS) determinations on four of these (Spillane *et al.*, 1989). Eighteen other monosubstituted phenylsulfamates were also synthesized by us at that time but comprehensive tasting analysis was not carried out. Now a further 16 compounds of this type have been made and characterized. In this paper we present our full results on all 34 compounds of type **I** (Table I) and formulate some structure–sweet taste relationships for the monosubstituted phenylsulfamate class of compounds.



Scheme I

MATERIALS AND METHODS

Amines

Precursor amines were generally obtained from Aldrich (Gillingham, Dorset, UK) except the following: *o*-ethylaniline, *p*-isopropylaniline, *p*-aminoacetophenone (Dottikon, Switzerland), *o*-isopropylaniline (Ethyl Corp.), *m*-aminophenol (BDH, Poole, UK), *o*-phenylenediamine (Hopkin and Williams, Essex, UK), *m*-phenylenediamine (Harrington Bros., London, UK).

Other chemicals used were obtained from sources previously cited (Spillane *et al.*, 1993).

Synthesis

Amines and reagents were distilled/recrystallized before use and dried. Sulfamates were synthesized and characterized by the procedures given previously (Spillane *et al.*, 1993). All the synthesized sulfamates were isolated as sodium salts (with one exception) and were analyzed

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for C, H and N and all, except the following, were found to have C, H and N within ± 0·5% of the theoretical:

		C	H	N
o-F	Theory	33·77	2·35	6·65
	Found	33·17	2·34	6 42
m-Cl	Theory	31·35	2·18	6 17
	Found	32·06	2·15	5·94
p-MeO	Theory	37·31	3·53	6·30
	Found	36·69	3·57	6·00
o-NO_2	Theory	29·96	2·09	11·80
	Found	30·75	2·20	11·90
m-CN.O.5H_2O	Theory	36·62	2·62	12·36
	Found	35·84	2·65	12·13
o-CN	Theory	38·12	2·70	12·87
	Found	37·95	2·29	13·95
p-CN	Theory	38·12	2·70	12·87
	Found	37·85	3·44	12·56
o-Et.1.5H_2O	Theory	38·40	5·20	5·60
	Found	38·58	5·86	5·18

Compound **I** (X = *m*-OK) was analysed for potassium content by atomic flame emission spectroscopy (FES) to distinguish between a *m*-OH or *m*-OK product, i.e. the compound could be either the monopotassium salt of *m*-hydroxylphenylsulfamic acid, *m*-$HOC_6H_4NHSO_3K$ or the *O*, *O*-dipotassium salt of *m*-hydroxyphenylsulfamic acid (**I**, X = *m*-OK). Using a standard calibration line for potassium (using KNO_3 standards) the K content for the present compound was 28·5%; required for the dipotassium salt was 29·4%. The monopotassium salt (**x** = *m*-OH) requires a K of 17·2%. This result together with the C, H and N results (Found: C, 27·70, H, 2·40, N, 5·27, $C_6H_5N0_4SK_2$ requires C, 27·18, H, 1·89, N, 5·28 while $C_6H_6NO_4SK$ requires C, 31·70, H, 2·64, N, 6·16) clearly indicate that the compound is a dipotassium salt. Two of the sulfamates prepared required modified procedures for their preparation and these are outlined here.

Preparation of compound ***I*** *(X =* m-*OK)*

The selective synthesis of either the *N*- or *O*-sulfonated derivatives of aminophenols has been investigated (Boyland & Manson, 1958) and a procedure has been developed for the synthesis of the *meta*-hydroxy sulfamate. This procedure was followed here. Chlorosulfonic acid (3·3 ml, 0·049 mol) was added dropwise to pyridine (25 ml, 0·309 mol) stirring at below 0°C. *m*-Amino phenol (5 g, 0·045 mol) dissolved in pyridine (40 ml) was added dropwise to the reaction mixture which was then kept stirring at room temperature overnight. After this time the mixture was poured into an aqueous solution of potassium hydroxide (7·5 g KOH in 100 ml water). The pH was adjusted to 6 using dilute hydrochloric acid and four ether extractions were carried out. The solution was then made alkaline (pH 9) using potassium hydroxide solution and evaporated to dryness under reduced pressure. The residue was extracted with hot methanol and the combined extracts evaporated to dryness. Repeated recrystallization from aqueous ethanol yielded the pure sulfamate in 39% yield.

Preparation of compound ***I*** *(X =* m-NH_2*)*

The following previously established procedure was used (Kamogawa *et al.*, 1982). *m*-Phenylenediamine (4·9 g, 0·045 mol) was dissolved in chloroform (30 ml) and the solution cooled to below 0°C. Chlorosulfonic acid (1 ml, 0·015 mol) was added dropwise with stirring keeping the temperature below 0°C. This required about 20 min. The reaction mixture was stirred for a further 30 min. below 0°C and then poured into a 6% sodium hydroxide solution (100 ml). The aqueous layer was separated and extracted four times with diethyl ether to remove the ether-soluble portion. The resulting aqueous layer was evaporated to dryness on the rotary evaporator. The crude product was extracted with 90% ethanol producing a white powder on cooling. Two further recrystallizations were required to purify the compound. Yield, 9%.

Taste panel procedure

Taste evaluation was carried out at a room temperature of 16 ± 0·5°C. Solutions for tasting were made up in volumetric flasks using distilled water and tasted within 24 hours of preparation. All samples were presented to an experienced group of panellists in clean, white plastic cups labelled A, B ... etc. A maximum of five solutions were given to panellists for judging at any one tasting session. Water rinses were always taken before and after the test solutions. All compounds were tasted as 0·01M solutions, a concentration found to give a readily detectable taste. All solutions were expectorated by the panellists.

In order to report the tastes properly, standards for the four primary tastes, sweet, sour, bitter and salty, were used. The concentrations of standards used are given in Table 1. Each standard was tasted at or above its recognition threshold (Best & Taylor, 1973; Paulus & Reisch, 1980) so that a definite taste was detected by each of the panellists.

Each of the tasters was first given a sample of each of the four 'primaries' followed by the sulfamate test solution. They were then asked to choose one or more of the four primary standards which best described the sulfamate solution being tasted. The aftertastes described refer to the taste sensation remaining after the test solution has been removed from the mouth (Horio & Kawamura, 1990). The results of the taste studies are reported in Table 2.

Table 1. Concentrations of the four primary taste standards

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

[a]BDH Chemicals
[b]Riedel de Haen.
[c]Quinine sulphate had to be stored in the dark as it is light-sensitive.

Table 2. Percentage of assessors (4) giving the taste quality[a] of monosubstituted phenylsulfamates

Sulfamate	Sweet	Sour	Bitter	Salt	Tasteless	Sweet aftertaste	Predominant taste (>50% Assessors)
o-Et	0	0	0	100	0	0	Salty
m-Et	50	0	25	0	25	50	Sweet and sweet aftertaste
p-Et	25	0	100	0	0	75	Bitter and sweet aftertaste
o-OEt	50	0	50	0	25	75	Bitter/sweet and sweet aftertaste
m-OEt	50	0	50	25	0	75	Bitter/sweet and sweet aftertaste
p-OEt	0	0	75	0	25	75	Bitter and sweet aftertaste
o-Pr^i	50	0	50	0	25	75	Bitter/sweet and sweet aftertaste
p-Pr^i	0	0	100	0	0	75	Bitter and sweet aftertaste
m-OK	0	0	100	0	0	0	Bitter
o-Me	25	0	100	0	0	75	Bitter and sweet aftertaste
m-COMe	0	0	100	0	0	0	Bitter
p-COMe	0	50	50	0	0	0	Bitter/sour
o-NH_2	0	0	0	100	0	0	Salty
p-Bu^n	0	0	100	0	0	0	Bitter
o-CF_3	0	0	100	0	0	50	Bitter and sweet aftertaste
m-NH_2	0	0	75	25	0	0	Bitter
o-F	0	50	50	25	0	0	Bitter/sour
p-F	0	0	100	0	0	50	Bitter and sweet aftertaste
o-Cl[b]	—	—	—	—	—	—	Aniline- or hydrocarbon-like taste
p-Cl	0	0	100	0	0	50	Bitter and sweet aftertaste
o-Br[b]	—	—	—	—	—	—	Aniline- or hydrocarbon-like taste
p-Br	25	0	75	0	0	50	Bitter and sweet aftertaste
o-I[b]	—	—	—	—	—	—	Aniline- or hydrocarbon-like taste
m-I[b]	—	—	—	—	—	—	Aniline- or hydrocarbon-like taste
p-I	25	0	100	0	0	75	Bitter and sweet aftertaste
o-MeO	25	0	100	0	0	50	Bitter and sweet aftertaste
m-MeO	75	25	50	0	0	25	Bitter/sweet
p-MeO	25	25	50	0	0	50	Bitter and sweet aftertaste
o-NO_2[b]	—	—	—	—	—	—	Aniline- or hydrocarbon-like taste
m-NO_2	0	25	100	0	0	0	Bitter
p-NO_2	0	100	0	25	0	0	Sour
o-CN	0	100	0	25	0	0	Sour
p-CN	25	0	100	0	0	50	Bitter and sweet aftertaste
m-CF_3	0	0	100	0	0	0	Bitter

[a]All of the above compounds were tasted as 0·01M solutions.
[b]These compounds displayed an aniline- or hydrocarbon-like taste and therefore were not given to the taste panel.

CPK Measurements

Corey–Pauling–Koltun (CPK) space-filling atomic models (Harte, 1969; Boyd, 1976; Barrett, 1979) were used for measurements of the length (x) width (z) and height (y) of the sulfamates using a previously defined procedure (Spillane & McGlinchey, 1981). Measurements were made on the aromatic portion (including the X substituent) only. Replicate measurements were at least within 5% (usually better). The values of x, y and z and of V_{CPK} are given in Table 3.

RESULTS AND DISCUSSION

The synthesis and tastant properties of 34 monosubstituted phenylsulfamates (**I**) are reported in this work. Eighteen of these sulfamates were made previously by us but synthetic details and information on their tastes have not been reported in our earlier preliminary communication (Spillane *et al.*, 1989). These details are now included here together with those of 16 additional materials, all of which are either *ortho*-, *meta*- or *para*-substituted phenylsulfamates.

Most of the sulfamates (see Materials and Methods) were synthesized and characterized by standard procedures. The yields were generally in the range of 20–40% (based on starting amine). The lowest yield was for the sulfamate **I** (X = *m*-NH_2), 9·3%; the highest for **I** (X = *p*-MeO), 61%. Taste data are recorded for all 34 compounds in Table 2. Five other sulfamates: **I** (X = *m*-F, *m*-Cl, *m*-Br, *m*-Me, *m*-CN) and the parent compound **I** (X = H) were also synthesized in our earlier study (Spillane *et al.*, 1989) but since the five *meta*-compounds were all quite sweet, relative sweetness (RS) was determined for four of them (**I**, X = *m*-CN could not be obtained sufficiently pure to include it in our assessment) and since the parent compound had already been assessed by Audrieth & Sveda (1944) these are not included in our present taste studies.

Combinations of tastes (multisapophoric molecules) are displayed by some of the compounds assessed (Table 2). The sweetness component displayed was much slighter than that found in the 'original' five *meta*-substituted compounds and only one compound, namely **I** (X = *m*-Et) displayed a sweet taste only. Bitterness accompanied sweetness in many cases. This phenomenon is well known and the occurrence of dual

bitter/sweet tastes has been observed in many different classes of compounds. The tastes of multisapophoric molecules, particularly those displaying simultaneous sweet and bitter tastes, have been reviewed (Verkade, 1968).

Models of the sweet and bitter taste receptor sites have been developed based on the structure-taste relationships of sweet and bitter isomers (Ciajolo *et al.*, 1983) . The occurrence of sweet and bitter taste among the simple amino acid enantiomers, (Solms *et al.*, 1965; Birch & Kemp, 1989), for example, led to the conclusion that the receptor sites for these two taste qualities must be similar two-dimensional structures.

A number of homologous series of compounds displaying sweet, bitter and bitter/sweet taste characteristics have been studied and models of the taste receptor active sites developed. A single model for both bitter- and sweet-tasting molecules was proposed as a result of the analysis of carboxylic acids, phenols, anilines, ureas, halogenated compounds, oxathiazionone dioxides and isothiazionone dioxides (Wieser *et al.*, 1977; Belitz *et al.*, 1979, 1981; Rohse & Belitz, 1988, 1990). This model describes the criteria for bitterness as being less restrictive than those for sweetness thus explaining why there are more bitter-tasting compounds than sweet-tasting compounds known. This was also found to be the case in the present work — 16 of the monosubstituted aromatic sulfamates exhibit some degree of sweetness, either predominant sweet taste or sweet aftertaste while 23 of the sulfamates displayed bitterness.

Sweet- and bitter-tasting dipeptides have also been classified in one model (Goodman *et al.*, 1987; Yamazaki *et al.*, 1991; Zhu *et al.*, 1992; Ando *et al.*, 1993). The proposed similarity between the receptor sites for sweet and bitter taste was supported by studies of the bitter/sweet perillartine molecules (Iwamura, 1980; Takahashi *et al.*, 1982, 1984). It was proposed that the bitter receptor can accommodate larger molecules than the sweet receptor which again limits the number of sweet-tasting molecules.

Studies of the effect of the hydrophile-lipophile balance (HLB) on taste (Daniel, 1989) also demonstrate the close relationship between sweetness and bitterness. Increasing the hydrophobicity of a sweet-tasting molecule generally tends to result in the occurrence of bitterness. The dividing line between sweet and bitter taste is very fine.

The mechanism of action of these compounds has been studied. Whether some of these molecules interact with the sweet receptor sites and some with the bitter receptor sites or whether one molecule can interact with both sites was investigated (Birch & Mylvaganam, 1976). It was concluded that one bitter/sweet molecule can span both taste receptors simultaneously if the sweet and bitter sapophores are at opposite ends of the molecule. More recently (Shamil *et al.*, 1987) it has been proposed that the compatibility of a multisapophoric molecule with water structure, as measured by the molecule's apparent specific volume, determines which is the predominant taste.

CPK measurements

We have successfully used Corey–Pauling–Koltun (CPK) molecular models to develop semi-quantitative structure-sweet taste relationships for carbo-(non-aromatic) (Spillane & McGlinchey, 1981), hetero- (Spillane *et al.*, 1983) and very recently disubstituted phenyl- (Spillane *et al.*, 1993) sulfamates. The volumes obtained, V_{CPK}, by use of these models have been shown to give good linear correlations with computed van der Waal's (V_w) and molecular (V_m) volumes (Spillane *et al.*, 1992). These V_{CPK} volumes are calculated by multiplying the individual length (x), width (z) and height (y) measurements made on the model so that $V_{CPK} = x.y.z$ and it can be thought of as the three-dimensional space into which the R portion of $RNHSO_3^-Na^+$ may have to fit in order to allow the Shallenberger mechanism, involving the sulfamate moiety itself, to operate successfully.

In previous work, plots of x(Å) vs V_{CPK} (Å^3) were found to discriminate between sweet and non-sweet

Table 3. CPK measurements for monosubstituted phensulfamates

Sulfamate	x(Å)	y(Å)	z(Å)	V_{CPK}(Å)^{3a}
o-Et	7·08	4·56	8·18	264·1
m-Et	5·86	4·47	7·56	198·1
p-Et	7·50	4·54	6·34	216·0
o-OEt	7·54	4·92	7·32	271·7
m-OEt	5·94	6·10	8·14	294·7
p-OEt	8·62	3·98	6·34	217·3
o-Pr^i	7·61	6·02	7·46	341·6
p-Pr^i	7·61	6·03	6·33	290·4
m-O	5·62	3·37	6·86	130·0
o-Me	6·67	3·72	7·52	186·9
m-COMe	6·33	3·74	8·57	202·7
p-COMe	7·73	3·73	6·32	182·2
o-NH_2	6·89	3·39	7·32	170·8
p-Bu^n	7·90	7·42	6·24	365·6
o-CF_3	7·46	4·68	7·78	271·8
m-NH_2	5·71	3·38	7·35	142·0
o-F	6·17	3·37	6·94	144·5
p-F	6·36	3·37	6·29	134·7
o-Cl	6·84	3·48	7·67	122·3
p-Cl	7·16	3·48	6·28	156·4
o-Br	7·06	3·77	7·94	211·4
p-Br	7·44	3·77	6·29	176·7
o-I	6·35	4·13	8·31	252·2
m-I	6·02	4·13	8·27	205·6
p-I	7·94	4·13	6·40	209·7
o-OMe	7·14	4·78	8·08	279·1
m-OMe	5·86	4·78	7·98	223·5
p-OMe	7·24	4·78	6·28	217·7
o-NO_2	6·47	4·83	7·56	235·2
m-NO_2	5·74	4·83	7·47	207·1
p-NO_2	7·13	4·83	6·33	218·1
o-CN	7·02	3·36	8·05	189·9
p-CN	7·55	3·36	6·28	159·4
m-CF_3	6·24	4·88	7·97	242·9
m-F	5·75	3·37	6·84	132·5
m-Cl	5·70	3·48	7·65	151·7
m-Br	5·74	3·77	7·92	171·6
m-CN	5·79	3·36	8·11	157·8
m-Me	5·76	3·71	7·39	157·8
H	5·77	3·37	6·33	122·9

[a] $V_{CPK} = x.y.z.$

sulfamates. Plots of this type which we tend to refer to as providing semi-quantitative SARs also have the advantage that they allow one to interpret, at least partially, sweetness/non-sweetness in physical (steric) terms.

In Table 3 the measured values of x, y and z are given together with the calculated V_{CPK} values for all 34 sulfamates and additionally for the five *meta*-substituted compounds previously examined and known to be relatively sweet and for the parent compound I (X = H). In Fig. 1 an x vs V_{CPK} plot of the 14 *meta*-substituted compounds in Table 3 has been made. From the point of view of sweetness these *meta*-compounds are the most important and the only really distinctly sweet compounds are found in this group. *Ortho*- and *para*-substituted sulfamates all lie above the *meta*-compounds in a x/V_{CPK} plot having x ranging from 6·47 (*o*-NO_2) to 8·62 (*p*-OEt) and the V_{CPK} values also vary considerably so a good deal of scatter is evident with no discernible line or curve that might be drawn to separate the different tastant categories being evident.

The eight *meta*-compounds displaying considerable (F, Cl, CN, Me, Br) and lesser (Et, OMe, OEt) sweetness all have $x = 5{\cdot}82 \pm 0{\cdot}12$ Å. Four other *meta*- compounds (O^-, COMe, I, CF_3) lie outside this range and are not sweet. The highly sweet compounds also have V_{CPK} between ~120 and ~170 Å^3 and although sweetness may be observed beyond this limit (up to at least ~295 Å^3) it is of a much lesser intensity. The lack of sweetness of the *m*-NH_2 (x = 5·71 V_{CPK} = 142·1) and *m*-NO_2 (x= 5·7, V_{CPK} = 207·1) compounds can be accounted for on an electronic basis (see below).

Hammett sigma values and sweetness

In Table 4 the σ_m values and predominant tastes are given for the 14 *meta*-sulfamates prepared and tasted. All of those displaying sweetness have σ_m in the range of –0·07 to + 0·56. Using the CPK measurements, specifically the x measurements, it has been possible to explain the sweetness/non sweetness of 12 *meta*-compounds. The lack of sweetness of *m*-NH_2 and *m*-NO_2 compounds could not be explained from the x/V_{CPK} plot. However these compounds have σ_m values of –0·16 and + 0·71 respectively and since these are outside the limits of –0·07 to + 0·56 they are not sweet.

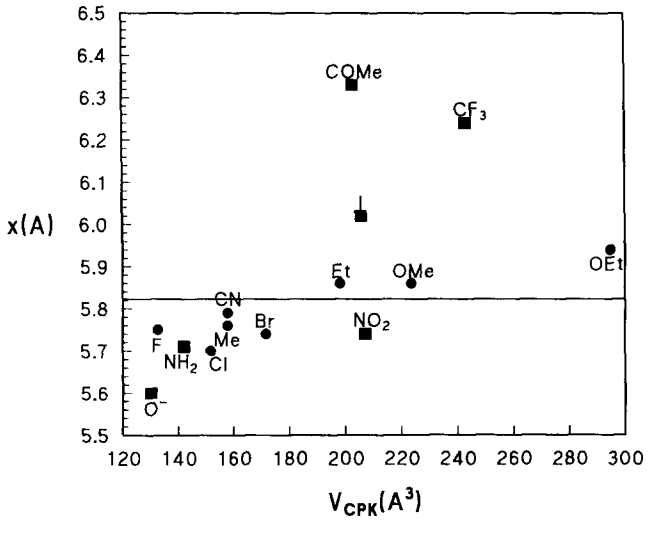

Fig. 1. Plot of x(Å) vs V_{CPK} (Å^3) for *meta*-substituted phenylsulfamates. (●) Sweet, (■) non-sweet.

Table 4. Hammett sigma values and tastes of *meta*-substituted phenylsulfamates

Substituent	Taste	σ_m[a]
Et	Sweet and sweet aftertaste	–0·07
OEt	Bitter/sweet and sweet aftertaste	0·10
COMe	Bitter	0·38
NH_2	Bitter	–0·16
O^-[b]	Bitter	–0·47[c]
F	Sweet	0·34
Cl	Sweet	0·37
Br	Sweet	0·39
I	Aniline or hydrocarbon-like	0·35
OMe	Bitter/sweet	0·12
NO_2	Bitter	0·71
CN	Sweet	0·56
CF_3	Bitter	0·43
Me	Sweet	–0·07

[a]McDaniel & Brown, 1958.
[b]This compound is assumed to exist in the dissociated form in solution.
[c]Hine, 1960.

Table 5. Hammett sigma values and tastes of *ortho*- and *para*-substituted phenylsulfamates

Substituent	Taste	Sigma
ortho-		σ_o
Et	Salty	–0·17[a]
OEt	Bitter/sweet and sweet aftertaste	–0·30[b]
Pr^i	Bitter/sweet and sweet aftertaste	–0·19[c]
Me	Bitter and sweet aftertaste	–0·12[a]
NH_2	Salty	–0·17[a]
CF_3	Bitter and sweet aftertaste	0·81[b]
F	Bitter/sour	1·20[a]
Cl	Anlline or hydrocarbon-like	1·20[a]
Br	Aniline or hydrocarbon-like	1·10[a]
I	Aniline or hydrocarbon-like	1·30[a]
MeO	Bitter/sweet and sweet aftertaste	0·60[a]
NO_2	Aniline or hydrocarbon-like	0·95[d]
CN	Sour	1·20[a]
para-		σ_p^e
Et	Bitter and sweet aftertaste	–0·15
OEt	Bitter and sweet aftertaste	–0·24
Pr^i	Bitter and sweet aftertaste	–0·15
COMe	Bitter/sour	0·50[f]
Bu^n	Bitter	–0·13
F	Bitter and sweet aftertaste	0·06
Cl	Bitter and sweet aftertaste	0·23
Br	Bitter and sweet aftertaste	0·23
I	Bitter and sweet aftertaste	0·18
MeO	Bitter and sweet aftertaste	–0·27
NO_2	Sour	0·78
CN	Bitter and sweet aftertaste	0·66

[a]Hess *et al.*, 1971.
[b]Tribble & Traynham, 1969.
[c]Obtained from a plot of σ_{star} versus σ_o.
[d]Thompson & Steel, 1956.
[e]McDaniel Brown, 1958.
[f]Jaffé, 1953.

This type of analysis can be extended and in Table 5 the σ_o values for the 13 *ortho*-substituted compounds and the σ_p values for the 12 *para*-substituted compounds together with the appropriate taste data are given. The five compounds displaying some sweet component all have σ_o in the range –0·30 to + 0·81; the other non-sweet compounds are outside this range. Two exceptions to this are *o*-Et (σ_o = –0·17) and *o*-NH_2 (σ_o = –0·17) both of which should be sweet.

A similar analysis of the 12 *para*-substituted sulfamates indicates that the compounds giving a sweet aftertaste (the only type of sweetness displayed) all have σ_p in the range –0·27 to + 0·66. Exceptions here are the *p*-COMe (σ_p = + 0·50) and *p*-Bu^n (σ_p = –0·13) both of which should show some sweetness on this basis.

The compound **I** (X = *m*-OK) was clearly shown to be a dipotassium salt (see Materials and Methods). However, the question remains that it could be of the form *m*-$HOC_6H_4N(K)SO_3K$ rather than *m*-$KOC_6H_4NHSO_3K$ as tacitly assumed here. We consider this to be unlikely because the pK_a value for the protonation equilibrium $RN\bar{S}O_3^- + H^+ = RNHSO_3^-$ is ~12 (Spillane *et al.*, 1982) whereas *meta*-substituted phenols are in the range ~10 → ~8·4 (Albert & Serjeant, 1984). Thus, the second potassium atom should be attached to the *meta*- OH rather than the –NH site.

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