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Synthesis and taste analysis of iminylsulfamates (hydrazonylsulfonates) of *N*-benzaldehyde, *N*-acetophenone, *N*-benzophenone and *N*-isobutyrophenone

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Thirty iminylsulfamates (hydrazonylsulfonates) $>C=NHSO_3^-Na^+$ have been synthesized via the precursor hydrazones. An array of taste portfolios were given by these materials and thus 15 compounds displayed predominant bitterness, five gave bitterness with a sweet aftertaste, three gave sourness with a sweet aftertaste, three were bitter/sour and one each were found to be predominantly sour, sweet, bitter/sour with a sweet aftertaste and extremely bitter (aniline- or hydrocarbon-like taste). Capacity factors, k_w, the pHs of the tastant aqueous solutions, the first-order molecular connectivities, $^1x^v$ and the length x, height y and width z of R in $RNHSO_3^-Na^+$ giving $V(xyz)$ were determined. No reliable structure–taste relationships were found.

INTRODUCTION

For some years we have been involved in extensive synthesis, tasting and analysis of sulfamates. A number of structure–taste relationships have been established from analysis of our own results and those of others (Benson & Spillane, 1976; Spillane & McGlinchey, 1981; Spillane & Sheahan, 1989; Spillane *et al.*, 1983, 1993, 1994). The compounds synthesized and assessed have been classified as carbo-, hetero- and mono- and disubstituted aromatic sulfamates (Spillane, 1993). Almost all of those made, to date possess $-\overset{|}{C}H-N(R)SO_3^-Na^+$ or $-\overset{||}{C}-N(R)SO_3^-Na^+$ (R usually $=$H) functionalities. Recently we have become interested in extending the basic sulfamate, $-NHSO_3^-$ function by synthesizing iminylsulfamates (hydrazonylsulfonates) of the type $-\overset{|}{C}=NHSO_3^-Na^+$. Here we report the syntheses of 30 such compounds, together with taste analysis of these.

MATERIALS AND METHODS

Materials

Microanalyses (C, H, N) were performed on a Perkin-Elmer elemental analyser PE 2400 and are within ±0.5% for compounds 1–4, except for the following: 1l. $1H_2O$ N 11.02, found 10.34; 1c. $0.5H_2O$ N 10.6, found 9.94; 1b. $1H_2O$ C 36.0, found 35.4; 1m. $0.5H_2O$ N 10.2, found 9.6; 2i. $1H_2O$ C 28.8, found 29.4; 2l. $2H_2O$ C 40.0, found 39.4; and 2m. N 9.46, found 11.6. Infrared (IR) spectra were measured on a Perkin-Elmer 983G spectrophotometer. ^{1}H- and ^{13}C-NMR spectra of the compounds were recorded on a Jeol 270 MHz spectrometer. The solvent used was DMSO-d_6.

Synthesis of hydrazones

The procedure is based on that of Lock and Stach (1944). *N*-Benzaldehyde hydrazones (precursors to compounds 1a–m) were obtained by refluxing, for approx 1.5 h, 0.1 mol aldehyde with 0.3 mol of hydrazine monohydrate dissolved in the minimum amount of absolute ethanol. Upon cooling, the resultant solution was extracted with ether and rotavaporated down to yield a pale yellow syrup. The syrup was freeze-dried to remove all traces of water.

The same method was employed for the synthesis of isobutyrophenone hydrazone (precursor to 4) and *N*-acetophenone hydrazones (precursors to 2a–m) except that a reflux time of 5 h was necessary.

N-Benzophenone hydrazones (precursors to 3a–c) were obtained by refluxing, for approximately 12 h, 0.1 mol of diaryl ketone with 0.4 mol of hydrazine monohydrate dissolved in the minimum amount of absolute ethanol. The solid hydrazones obtained on cooling were recrystallized several times from hot ethanol.

Syntheses of iminylsulfamates

The procedure was based on that of Sureau & Obelliane (1957) with some modifications. Chlorosulfonic acid was added dropwise with stirring to excess dry α-picoline (10 M excess) at $\leqslant 0$°C. This was followed by addition of the liquid hydrazone (equimolar with chlorosulfonic acid) or solution of the solid hydrazone in α-picoline, dropwise, with stirring.

The resultant mixture was heated to 70–80°C in an oil bath and stirred for 1 h. After stirring at room temperature overnight the solution was basified using 2 M NaOH and the unreacted hydrazone 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 iminylsulfamate (sodium salt).

Slight changes were made to the above procedure in the synthesis of *N*-benzaldehyde iminylsulfamates, 1a–m.

1. Double the amount of chlorosulfonic acid with a large excess of α-picoline was used as this seemed to increase the yield of iminylsulfamate without causing disulfamation.
2. The α-picoline–sulfur trioxide complex was stirred at room temperature for 1 h before the addition of the hydrazone. Care had to be taken to avoid contamination of the hydrazone with acid fumes which promote azine formation.

Characterization of iminylsulfamtes, 1–4

All the synthesized sulfamates gave positive, clean (free of chloride and sulfate ions) sulfamate tests. As is normal with sulfamates, most had some occluded water of recrystallization. All gave satisfactory elemental analyses except the six compounds listed above which were just outside the limits set for one of the three elements (C, H, N).

Compounds 1–4 showed the following common IR bands: 730–660 $V_{\text{N-S}}$, 1070–1040 V_{SO_3} (sym.), 1203–1170 V_{SO_3} (sym.), 1240–1210 V_{SO_3} (asym), 1660–1610 $V_{\text{C=N}}$ and 3400–3190 $V_{\text{N-H}}$ (cm^{-1}). ^{1}H and ^{13}C NMR data for three representative compounds are given: ^{1}H for 1c, 3.5 (s, CH), 7.48–7.65 (m, ArHs), 7.97 (s, NH); ^{13}C, 127.3–128.5 (ArCs), 135.2 (C–Cl), 138 (C=N); ^{1}H for 2f, 2.13 (s, CH_3), 7.45–7.81 (m, ArHs), 8.3 (broad s, NH); ^{13}C 12.67 (CH_3), 127.2–127.9 (ArCs), 132.3 (C–Cl), 143.1 (C=N); ^{1}H for 3c, 7.33–7.42 (ArHs), 7.73 (s,NH); ^{13}C, 126.3–128.1 (ArCs), 137.7 (C–Cl), 145.0 (C=N).

Capacity factor (k_w) measurements for 1–3a, 4

The k_w values were determined in this laboratory by reversed-phase HPLC using a Techopak 10C18 column. A Milton Roy CM4000 multiple solvent delivery system and an Altex refractive index detector were used in the determination. A flow rate of 0.5 ml/min was maintained and the eluant was water.

KBr was used as a standard in each run and k_w was calculated from the following equation:

$$k_w = (t_{\text{ArC(R)NNHSO}_3{}^-\text{Na}^+} - t_{\text{KBr}})/t_{\text{KBr}},$$

where $t_{\text{ArC(R)NNHSO}_3{}^-\text{Na}^+}$ is the retention time of the iminylsulfamate in question and t_{KBr} is the retention time of potassium bromide used as a standard.

Calculation of first-order molecular connectivity (^{1}x^v)

Values of ^{1}x^v were calculated for the sulfamate anion, i.e. $RNHSO_3^-$ portion of each salt (Spillane *et al.*, 1983) using the valence delta 'σ^v' values reported (Kier & Hall, 1976).

Measurement of *x*, *y*, *z* and *V*

These measurements were carried out as described previously (Spillane & McGlinchey, 1981) using the R portion of the sulfamate, $RNHSO_3^-Na^+$.

Taste analysis of iminylsulfamates 1–4

The procedure was identical with that recently described (Spillane *et al.*, 1994) The concentrations of the four primary standards used are shown in Table 1.

RESULTS AND DISCUSSION

There are only a few examples in the literature where the sulfamate function has been extended by the addition of a nitrogen atom -N–$NHSO_3H$. Thus, hydrazine monosulfonic acid, NH_2NHSO_3H and some other hydrazinesulfonic acids have been prepared (Baumgarten, 1926; Audrieth & West, 1955; Meuwsen & Tischer, 1958). Also the azidodisulfamate, $KO_3SN=NSO_3K$ has been reported (Konrad & Pellens, 1926). Six compounds of this general type have been synthesized to examine their tastant properties. They are *N*-piperidinyl-, *N*-morpholino- (Benson & Spillane, 1976), *N*-azacycloheptyl (Spillane *et al.*, 1983), *N*-pyrrolo-, *N*-1-methylpiperazinyl- and *N*-phthalimidosulfamates (De Nardo *et al.*, 1984). We have not been able to find any examples of iminylsulfamate systems.

Table 1. The concentrations of the four primary standards

Standard	Concentration
Sucrose	4.4×10^{-2} M (1.5%)
Citric acid	4.76×10^{-4} M (0.01%)
Quinine sulphate	6.1×10^{-6} M (0.0005%)
Sodium chloride	3.4×10^{-2} M (0.2%)

Table 2. Yields, taste analysis, pH, capacity factors, first-order molecular connectivities and volumes of *N*-benzaldehyde, *N*-acetophenone-, *N*-benzophenone- and *N*-isobutyrophenone iminylsulfamates (hydrazonylsulfonates)

Compound No.[a]	X	Y	Yield (%)	Taste analysis[b]						Predominant taste[c] (> 50% assessors)	pH[d]	log k_w	$^1\chi^v$	V(Å^3)
				Sweet	Sour	Bitter	Salt	Tasteless	Sweet aftertaste					
1a. $1H_2O$	H	H	12.3	0	60	40	0	0	60	Sour + s.a.	3.50	0.0914	3.593	189.14
1b. $1H_2O$	H	CH_3	25.7	20	60	40	0	0	60	Sour + s.a.	3.70	0.4283	4.004	211.22
1c. $0.5H_2O$	H	Cl	18.5	0	60	60	0	0	80	Bitter/sour + s.a.	3.45	0.4830	4.106	231.26
1d. $1H_2O$	Cl	H	12.1	0	40	80	0	0	80	Bitter + s.a.	4.15	0.467	4.106	239.31
1e. $2H_2O$	H	OCH_3	21.2	20	40	60	0	0	80	Bitter + s.a.	3.70	0.3502	4.116	291.38
1f. $1H_2O$	OCH_3	H	15.1	0	60	60	20	0	40	Bitter/sour	6.00	0.4084	4.116	358.44
1g. $O.5H_2O$	H	Br	15.7	0	20	100	0	0	60	Bitter + s.a.	3.40	0.5805	4.496	237.33
1h. $1H_2O$	Br	H	32.6	0	40	80	0	0	40	Bitter	4.30	0.5659	4.496	282.43
1i. $1H_2O$	H	F	10.9	0	20	80	0	0	60	Bitter + s.a.	6.00	0.1560	3.392	205.61
1j. $1H_2O$	H	C_2H_5	21.4	0	100	40	0	0	0	Sour	5.90	0.7010	4.567	292.55
1k. $1H_2O$	H	C_3H_7	22.8	0	60	60	20	0	0	Bitter/sour	6.05	0.9510	4.948	360.02
1l. $1H_2O$	OCH_3	OCH_3	8.8	0	20	80	0	0	0	Bitter	6.20	0.5090	4.645	389.74
1m. $O.5H_2O$	H	OC_2H_5	12.5	100	0	40	0	0	0	Sweet	5.85	0.6317	4.704	309.56
2a. $1H_2O$	H	H	10.7	0	0	100	0	0	0	Bitter	5.00	0.2949	4.020	225.52
2b. $1.5H_2O$	H	NO_2	19.1	0	40	80	0	0	0	Bitter	4.50	0.5518	4.468	278.18
2c. $1H_2O$	NO_2	H	23.9	0	0	100	0	0	20	Bitter	5.75	0.5093	4.468	333.60
2d. $1H_2O$	H	CH_3	8.6	0	20	80	0	0	20	Bitter	4.75	0.6359	4.431	244.99
2e. $1H_2O$	CH_3	H	24.7	0	20	80	0	0	20	Bitter	5.20	0.6157	4.431	267.85
2f. $1H_2O$	H	Cl	26.8	0	20	100	0	0	0	Bitter	4.85	0.6599	4.533	265.89
2g. $1H_2O$	H	OCH_3	18.6	0	40	60	20	0	20	Bitter	5.15	0.5851	4.543	294.80
2h. $1H_2O$	OCH_3	H	14.2	20	80	40	0	0	80	Sour + s.a.	6.00	0.6135	4.543	358.92
2i. $1H_2O$	H	Br	15.8	0	20	100	0	0	0	Bitter	4.80	0.7605	4.923	274.19
2j. $1H_2O$	Br	H	35.9	0	40	100	0	0	60	Bitter + s.a.	4.80	0.7255	4.923	290.52
2k. $1H_2O$	H	F	39.5	0	40	60	0	0	0	Bitter	5.70	0.3605	4.812	242.33
2l. $2H_2O$	H	C_2H_5	14.1	0	60	60	0	0	40	Bitter/sour	5.60	0.8626	4.991	324.74
2m.	OCH_3	OCH_3	10.7	0	20	100	0	0	20	Bitter	6.35	0.7047	5.072	395.51
3a. $3H_2O$	—	H	28.4	0	20	80	0	0	0	Bitter	4.25	1.2027	5.681	486.65
3b. $2H_2O$	—	CH_3	27.0	0	0	100	0	0	20	Bitter	4.20	—[e]	6.092	515.19
3c. $O.5H_2O$	—	Cl	16.7	0	0	100	0	0	20	Bitter	4.10	—[e]	6.194	549.88
4. $2H_2O$	—	—	18.9	—	—	—	—	—	—	Aniline or hydrocarbon like	6.65	0.900	4.964	365.54

[a] The amount of water of crystallization that the sulfamates have crystallized with is indicated.

[b] Five assessors were used for each solution. The percentage of assessors giving the particular taste quality is given in the columns.

[c] s.a. = sweet aftertaste.

[d] Using 0.01 M solutions for tasting.

[e] Could not be measured because of excessively long retention times.

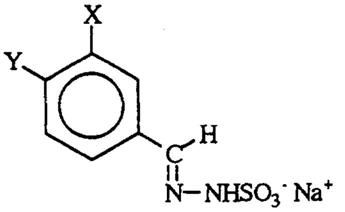
In the present work we have synthesized 30 iminylsulfamates (hydrazonylsulfonates) from the appropriate hydrazones which were synthesized from the corresponding aldehydes and ketones, all of which were commercially available. The sulfamates have been fully characterized and, in Table 2, data on all 30 are presented. Figure 1 shows the corresponding structures. In Table 2 the amounts of water of crystallization, the % yields, the pH of the solutions for tasting, the capacity factors for the sulfamates (k_w), the calculated first-order molecular connectivities and the calculated volumes, V, are given.

Full results of the taste analysis on each compound are also given. The 'taste spectra' of these compounds displayed varying per cents of all four primary tastes. The columns in Table 2 headed 'taste analysis' give the percentage of assessors which found each specified taste. The last of the 'taste analysis' columns summarizes the predominant taste.

Search for structure–taste relationships.

As in much of our previous work in this area, we measured the dimensions of R in R-NHSO$_3^-$ using

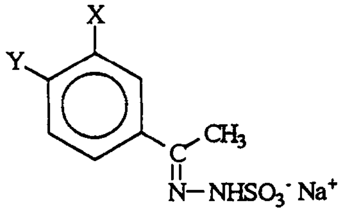
N-Benzaldehyde iminylsulfamates



1

1a X = H, Y = H
b X = H, Y = CH$_3$
c X = H, Y = Cl
d X = Cl, Y = H
e X = H, Y = OCH$_3$
f X = OCH$_3$, Y = H
g X = H, Y = Br
h X = Br, Y = H
i X = H, Y = F
j X = H, Y = C$_2$H$_5$
k X = H, Y = C$_3$H$_7$
l X = OCH$_3$, Y = OCH$_3$
m X = H, Y = OC$_2$H$_5$

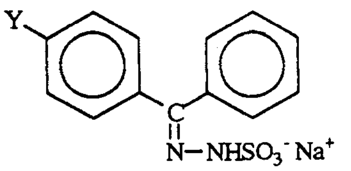
N-Acetophenone iminylsulfamates



2

2a X = H, Y = H
b X = H, Y = NO$_2$
c X = NO$_2$, Y = H
d X = H, Y = CH$_3$
e X = CH$_3$, Y = H
f X = H, Y = Cl
g X = H, Y = OCH$_3$
h X = OCH$_3$, Y = H
i X = H, Y = Br
j X = Br, Y = H
k X = H, Y = F
l X = H, Y = C$_2$H$_5$
m X = OCH$_3$, Y = OCH$_3$

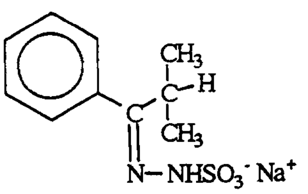
N-Benzophenone iminylsulfamates



3

3a Y = H
b Y = CH$_3$
c Y = Cl

N-Isobutyrophenone iminylsulfamate



4

Fig. 1. Structures of compounds 1–4.

Corey–Pauling–Koltun (CPK) models. However, plots of x, the length of R vs V, its volume and similar type plots utilizing y, the height of R and z, the width of R gave considerable scatter and were not pursued.

Using the pH values, k_ws and $^1x^v$ values either singly or in combination with V did not produce any clear-cut structure–taste relationships.

Since only four compounds displayed sourness, no attempt was made to derive a structure–taste relationship for these. Of the four primary tastes, saltiness was almost completely absent in these sulfamates.

Summary

Thirty new iminylsulfamates have been synthesized and tasted. The predominant tastes displayed by these compounds were bitterness, sourness and either sweet aftertaste or sweetness. Very little saltiness was detected in any of the new materials.

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