specifically to mimic the morphine structure did overlap more with it, but none were energetically favored. The minimum energy protonated conformer resembled calculated low-energy conformers of meperidine in several key respects.

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Structure–Activity Studies on Sulfamate Sweeteners

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The structure–activity relationships governing sulfamate sweeteners are reviewed under the headings: size of the reduced ring, changes in the sulfamate function, substitution of hydrogen in the ring, and substitution of carbon in the ring and open-chain compounds. Fifteen compounds have been synthesized with a view to testing the limitations on structural changes which may be made within these categories without loss of sweetness. The presence of the grouping $>CHN(R)SO_3^-$ is suggested as a necessary but not a sufficient condition for a compound to be sweet-tasting. Thus, the B center of the Shallenberger A–H,B theory of sweetness is best regarded as being $-SO_3^-$ rather than $-SO_2-$ for sulfamates. Threshold levels and relative sweetness have been determined for seven sulfamates.

Following the accidental discovery of the sweetening properties of cyclamate (**1d**) by Sveda in 1937, Audrieth and Sveda[1] carried out a limited structure–activity study, synthesizing and screening for sweetness a number of compounds containing the sulfamate functional group. From this study they concluded that the groups essential for sweetness were "(a) a cyclohexyl ring which may or may not be substituted and (b) a free hydrogen on the nitrogen of the sulfamate function $-NHSO_3X$, where X may be almost any salt-forming group". In succeeding years many groups[2-12] have synthesized sweet-tasting sulfamates, many of which require qualification of the rules formulated by Audrieth and Sveda and, in some cases, require an extension or are at variance with them. Clearly then a reappraisal of the structure–activity relationships of sulfamate sweeteners is necessary and we suggest that these relationships are best categorized under the headings: size of the reduced ring, changes in the sulfamate function, substitution of hydrogen atoms of the ring and of carbon atoms of the ring, and opening of the reduced ring (i.e., aliphatics). In this present study the 15 sulfamates which we have synthesized and characterized have been designed to test some of the limitations on structural changes which may be made within these categories without loss of sweetness.

Chemistry. All primary sulfamates, i.e., those containing the $-NHSO_3^-$ group, were synthesized by reaction of the corresponding amine with chlorosulfonic acid.[1] Secondary sulfamates were prepared from the appropriate primary amines by methylation[13] followed by sulfamation with chlorosulfonic acid. Cyclohexylsulfamyl chloride was prepared by reaction of cyclohexylsulfamic acid with phosphorus trichloride.

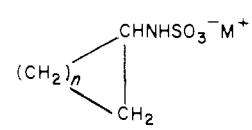
Structure–Activity Relationships and Discussion. Size of the Reduced Ring. Variation in the size of the reduced ring is an obvious starting point in a probe of the

effect of structure on sweetness. Some years ago, Beck[3] has shown that *N*-(3-methylcyclopentyl)sulfamate is almost as sweet as cyclamate, a finding confirmed by Unterhalt and Boschemeyer,[7] who also repeated earlier work[4] and synthesized the unsubstituted, sweet cyclopentylsulfamate (**1c**). Enlargement of the reduced ring does not cause the disappearance of the sweet taste either since both *N*-cycloheptyl- (**1e**) and *N*-cyclooctyl- (**1f**) sulfamates[2,7] are reported to be sweet-tasting. *N*-Cyclononylsulfamate (**1g**) is only faintly sweet[7] and we suspected that further increase in ring size would destroy sweetness totally. We confirmed that this was so by synthesizing *N*-cyclododecylsulfamate (**1h**). Further decrease in the size of the reduced ring also leads to loss of sweetness and we have found that both *N*-cyclobutyl- (**1b**) and *N*-cyclopropyl- (**1a**) sulfamates are tasteless. Unterhalt and Boschemeyer have also made and confirmed[7] that **1a** is not sweet and Hamprecht et al.[14] have synthesized **1b** but did not check for sweetness. We were particularly interested in **1b** because we had predicted[15] and recently confirmed that the stability of its nitrogen–sulfur bond to in vitro hydrolysis was greater than that of the parent cyclamates. Had this compound been sweet we would have included it among those sulfamates with which we are now carrying out in vivo feeding experiments to study the possible metabolites of other sweet sulfamates.

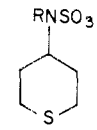
Insertion of a methylene group between the sulfamate function and the reduced ring causes loss of sweetness in **1d**,[8] a finding which we have confirmed, but, surprisingly, if the reduced ring is **1c**, then sweetness is retained.[12] *N*-Cyclopentylmethylsulfamate cannot liberate an amine in which the amino group is directly attached to the ring and thus the French workers who have made it suggest that it is unlikely to induce carcinogenic effects.

Changes in the Sulfamate Function. Audrieth and Sveda[1] showed, by synthesizing *N*-methyl- and *N*-ethyl-*N*-cyclohexylsulfamates and *N*,*N*-dicyclohexylsulfamate, that the presence of a hydrogen atom on the nitrogen of the sulfamate function was essential for sweetness. We have confirmed this in a different way by synthesizing *N*-methyl-*N*-isobutyl- and *N*-methyl-*N*-cycloheptylsulfamate, neither of which retains the sweetness of the unmethylated compounds. The retention of the amino hydrogen is not a necessary condition for sweetness in cyclamate-analogous sulfur heterocycles. Thus, tetrahydro-2*H*-thiopyran-4-sulfamic acid (**2a**) and tetrahydro-2*H*-thiopyran-4-sulfamic acid 1,1-dioxide (**3a**) and compounds **2** with R = ethyl, *n*-butyl, and 2-hydroxyethyl and compounds **3** with R = ethyl and *n*-butyl are sweet.[10] From the point of view of sweetness we believe that the more crucial part of the sulfamate anion is the $-SO_3^-$ moiety, which can act as a B center in the Shallenberger A–H,B theory of sweetness.[16] Tampering with this section of the sulfamate function destroys sweetness since *N*-cyclohexylsulfamyl chloride is tasteless. Thus, it is more satisfactory to regard $-SO_3^-$, rather than $-SO_2-$,[16] as being the B center.

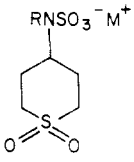
Substitution of Hydrogen in the Ring. In general substitution at the 2–6 positions in **1d** by one or two methyl (or ethyl) groups does not destroy sweetness.[3,7,8] In **1c** ring substitution by a methyl group at the 2 or the 3 positions does not impair sweetness. However, substitution by methyl at position 1 of either **1d** or **1c** destroys the sweetness of these compounds.[8] This suggests that the presence of at least one hydrogen atom α to the sulfamate function is important and it is significant that *every* known sulfamate sweetener contains the system, $>CHN(R)SO_3^-$. As a partial test of our hypothesis we have synthesized *N*-(1-adamantyl)sulfamate (**4**) and find that it is not sweet, which can be rationalized in terms of the postulated α-hydrogen requirement.



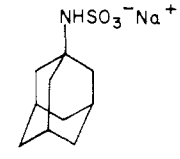
1a, *n* = 1
b, *n* = 2
c, *n* = 3
d, *n* = 4
e, *n* = 5
f, *n* = 6
g, *n* = 7
h, *n* = 10



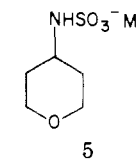
2a, R = H
b, R = C_2H_5, $CH_3(CH_2)_2$, $HOCH_2CH_2$



3a, R = H
b, R = C_2H_5, $CH_3(CH_2)_3$



4



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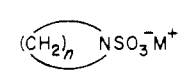
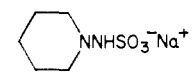
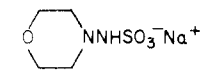


6a, *n* = 4
b, *n* = 6
c, *n* = 7
d, *n* = 8



7



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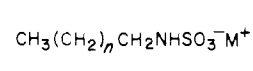
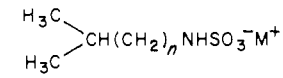


9a, *n* = 1
b, *n* = 2
c, *n* = 4
d, *n* = 6
e, *n* = 13
f, *n* = 16



10a, *n* = 0
b, *n* = 1
c, *n* = 2

Substitution of Carbon of the Ring. Substitution of the carbon atom at position 4 in **1d** by oxygen gives **5** which is not sweet.[9] The series of compounds (**6**) prepared by sulfamation of pyrrolidine, hexa-, hepta-, and octamethyleneimines, are not sweet.[2] We have prepared a representative "true" sulfamate of these compounds to give **7** which is not sweet. We also prepared *N*-morpholinesulfamate (**8**) which is tasteless. As pointed out above, however, substitution by sulfur either as a sulfur atom or as the $-SO_2-$ function giving rise to **2** and **3**, respectively, does not destroy sweetness.

Open Chain Compounds. Audrieth and Sveda[1] prepared *N*-*n*-hexylsulfamate (**9c**), which was not sweet, and concluded that a reduced ring was necessary for sweetness. However, in 1964, Yamaguchi prepared *N*-isobutyl- (**10b**) and *N*-isoamyl- (**10c**) sulfamates[5] and *N*-*n*-butylsulfamate (**9b**),[6] all of which were sweet. Unterhalt and Boschemeyer[8] and very recently French workers[11] have confirmed the sweetness of these branched sulfamates. The French group have also checked the sweetness of **9b** and they also report that **9a** is faintly sweet. All the other straight-chain sulfamates made (up to **9d**) were tasteless. Longer chain sulfamates, e.g., **9e**[17] and **9f**,[18] are not sweet either though they are useful as surface active agents. We have confirmed that **9a**, **9b**, and **10b** are sweet and that **10a** and *sec*-butylsulfamate are not sweet. Both the French group and the German workers have found that methyl-2-butylsulfamate is sweet. The French workers have synthesized quite a number of other branched sulfamates but the only sweet material found was

Table I. Recognition Thresholds for Seven Sweet Sulfamates

Compd[a]	Threshold level, mol/l.[b]	Mean threshold ± SD, mol/l.[c]	Range sampled, mol/l.
1d (8)	0.0023	0.0046 ± 0.0023	0.0373 → 0.0005
1e (8)	0.0014	0.0038 ± 0.0020	0.0465 → 0.0003
1f (8)	0.0010	0.0035 ± 0.0005	0.0436 → 0.00007
1c (8)	0.0033	0.0096 ± 0.0044	0.0534 → 0.0002
10b (6)	0.0100	0.0250 ± 0.0100	0.1605 → 0.0056
9b (7)	0.0380	0.0462 ± 0.0095	0.1142 → 0.0035
9a (5)	0.0310	0.1240 ± 0.0850	0.4037 → 0.0310

[a] The numbers in parentheses give the number of tasters for each compound. [b] The values are the lowest perceptible taste levels recorded for each compound by one or more tasters. [c] The values are the pooled means ± standard deviation (SD) of all the tasters.

N-neopentylsulfamate. We have confirmed that *N*-*tert*-octylsulfamate[11] is not sweet.

Relative Sweetness. We have assessed threshold levels (Table I) and relative sweetness (RS) (Table II) for seven sulfamates including compound **1d**. The threshold level and RS (compared to other sweeteners—both nutritive and nonnutritive) of **1d** have been determined previously,[1,19] but reliable threshold levels have not been determined for other sulfamates (with the exception of *o*-Me-**1d**[1]). RS values have been determined for six sulfamates.[11] The compounds in Tables I and II were generally similar in taste response to **1d**; however, compounds **9a** and **9b** also gave a saline and sometimes bitter taste which tended to mask the prolonged sweet taste noted with the other sulfamates. The sweetness sulfamates are those containing alicyclic rings (see Table II) and a spread of RS of about 60 exists between the sweetest alicyclic compound (**1d**) and the least sweet aliphatic compound (**9a**).

Conclusions

The structure–activity relationships governing sulfamate sweeteners can conveniently be examined under the five headings given above. The vital factor for sulfamate sweetness appears to be the presence of the system $>CHN(R)SO_3^-$, in which there may be one or two α-hydrogens. The presence of this system appears to be a necessary but not a sufficient condition for sweetness. Such a system can also account for the sweetness of compounds **2b** and **3b** which lack an amino hydrogen. The postulated involvement of this system also finds a formal analogy with Shallenberger and Acree's[20] contention that it is the ortho hydrogens to the nitro groups and not the amino hydrogens of the nitroaniline sweeteners that act as the proton of the AH,B model ($-CH{=}CNO_2$).

Experimental Section

Ir spectra were measured as Nujol mulls on a Perkin-Elmer 377.

Sulfamate Syntheses. All the sulfamates were synthesized by the same general procedure involving reaction of the appropriate amine with chlorosulfonic acid. The following synthesis of **1b** is typical.

Cyclobutylamine (1.678 g, 0.023 mol) was dissolved in 25 ml of dry chloroform in a 50-ml three-necked flask equipped with a mechanical stirrer, HCl gas trap, and a dropping funnel. The solution was cooled to 0° in an ice-water bath and chlorosulfonic acid (0.48 ml, 0.007 mol) was added slowly keeping the temperature as near as possible to 0°. The solution was stirred for 2 h after which the chloroform was removed under reduced pressure. The residue was added to a solution of 0.014 mol of NaOH in 30 ml of water and stirred. The liberated cyclobutylamine was extracted with 2 × 25 ml of ether (and later recovered) and the aqueous phase concentrated to yield white crystals of **1b** which were collected and recrystallized twice from

Table II. Relative Sweetness of Seven Sulfamates Compared to a 3% (w/v) Sucrose Solution[a]

Compd	Range sampled, mol/l.	Concentration equivalent[c] mol/l.	Concentration equivalent[c] mg/ml	Rel sweetness[d]
1d	0.0497 → 0.0004	0.0035 ± 0.0004	0.720 ± 0.096	41.00
1e	0.0930 → 0.0018	0.0040 ± 0.0004	0.880 ± 0.096	34.09
1f	0.0262 → 0.0017	0.0047 ± 0.0011	1.080 ± 0.256	27.77
1c	0.1069 → 0.0021	0.0160 ± 0.0064	3.000 ± 1.200	10.00
9b	0.3582 → 0.0035	0.0490 ± 0.0161	8.580 ± 2.830	3.49
10b	0.1412 → 0.0338	0.0584 ± 0.0060	10.340 ± 1.064	2.90
9a	0.4037 → 0.0310	0.2185 ± 0.0636	35.20 ± 10.240	0.63[b]

[a] Five tasters were used for each compound. [b] Because of the high threshold value for this compound (see Table I) its relative sweetness (RS) was assessed against a 1.5% (w/v) sucrose solution. The value obtained (0.462) was multiplied by a factor (1.373) in order to compare its sweetness to the 3% standard solution. This factor was calculated as follows. The RS of 1d was assessed against 1.5% (RS = 25.72), 2% (RS = 31.20), and 3% (RS = 41.0) and a plot of RS against percent sucrose was approximately linear. Factors were calculated by the following divisions, 41/25.72 = 1.594, 41/31.2 = 1.314, and 31.2/25.72 = 1.213, and these were averaged to give 1.373. [c] The values are the pooled means ± SD of the concentration deemed to be equal to the standard (3%) solution. [d] RS is defined as the concentration of the standard sucrose, mg/ml, i.e., 30/the concentration of equivalent sulfamate solution, mg/ml.

Table III. Synthesis and Percent Yields of Sodium Sulfamates

Compd	Formula[a]	% yield	Ref	Compd	Formula	% yield	Ref
1a	$C_3H_6NO_3SNa$	36	7	9b	$C_4H_{10}NO_3S$	34	11
1b	$C_4H_8NO_3SNa{\cdot}1H_2O$	25	14	10a	$C_3H_8NO_3SNa$	21	11, 26
1h	$C_{12}H_{24}NO_3SNa{\cdot}1H_2O$	32	This work	*N*-Me-1e	$C_8H_{16}NO_3SNa{\cdot}0.5H_2O$	20	This work
4	$C_{10}H_{16}NO_3SNa{\cdot}2H_2O$	36	This work	*N*-Me-10b	$C_5H_{12}NO_3SNa{\cdot}1.5H_2O$[b]	20	This work
7	$C_5H_{11}N_2O_3SNa{\cdot}1H_2O$	31	This work	*N*-Me-1d	$C_5H_{14}NO_3SNa$	43	11
8	$C_4H_9N_2O_4SNa{\cdot}0.5H_2O$	30	This work	*s*-Bu-	$C_4H_{10}NO_3SNa$	37	11, 14, 27
9a	$C_3H_8NO_3SNa$	35	This work	*tert*-Octyl-	$C_8H_{18}NO_3SNa{\cdot}1.5H_2O$	21	11

[a] All compounds were analyzed for C, H, and N except *tert*-octylsulfamate, which was analyzed for C and H only. All analyses were within ±0.4% of calculated values unless otherwise stated. Despite drying in vacuo over phosphorus pentoxide for several days it was not possible to remove all the water of recrystallization. Occluded solvent of recrystallization is a common problem with all sulfamates.[1,11,21,22] [b] C: calcd, 27.8; found, 27.2. H: calcd, 6.91; found, 6.2. N: calcd, 6.48; found, 7.2.

ethanol. The recrystallized material was dried in vacuo over phosphorus pentoxide for several days. 1**b** gave negative tests for chloride ion (silver nitrate) and sulfate ion (barium chloride) and a positive sulfamate test (white precipitate of barium sulfate on boiling for 1 h an acidified aqueous–dioxane solution of 1**b** and then adding barium chloride solution). Details of all the sulfamates prepared are given in Table III. The ir spectra of all the sulfamates displayed the following bands: 3400–3190 (v NH), 1238–1210 (ν_{asym} SO_3), 1203–1170 (ν_{sym} SO_3), 1072–1040 (ν_{sym} SO_3), and 730–660 (v NS).[11,23] Percent yields were based on the assumption that one-third of the amine reacted to give sulfamate.

Syntheses of *N*-Methylisobutylamine and *N*-Methylcycloheptylamine. The procedure described for the synthesis of *N*-methyl-*n*-butylamine[13] was followed. The yield of *N*-methylisobutylamine was 62%, bp 76–78° (lit.[24] 76–78°), and of *N*-methylcycloheptylamine was 56%.

Synthesis of *N*-Cyclohexylsulfamyl Chloride. Cyclohexylsulfamic acid (53.7 g, 0.3 mol) was suspended in 200 ml of dry carbon tetrachloride and phosphorus trichloride (53 g, 0.3 mol) was added. After the initial vigorous reaction had subsided the mixture was stirred for 10 h at 80°. The reaction mixture was cooled and carbon tetrachloride was removed under reduced pressure. Solids remaining were filtered off and the residue was fractionally distilled under reduced pressure. The fraction collected at 136–140° (0.2 mmHg) [lit.[25] 120° (0.1 mmHg)] on standing crystallized out yielding 34.1 g (61%). Anal. ($C_6H_{12}ClNO_3S$) C, H, N.

Determination of Threshold Levels and Relative Sweetness (RS). A pool of 12 tasters was used in selecting panels for threshold and RS determination. All solutions were made up with distilled water and all testing was carried out at room temperature, 20–22 °C.

In the threshold determination nine solutions of varying concentration over the range started in Table I were dispensed in 8-ml aliquots and presented to the tasters in a randomized (concentration) manner. In the determination each taster was asked to decide (a) whether or not a solution was sweet and (b) to note any other taste sensation, e.g., bitterness or salinity. Between samples tasters were required to rinse out their mouths with distilled water.

RS was determined as follows. Each taster was asked to compare the level of sweetness of 8-ml aliquots of sulfamate solutions of varying concentrations, over the range stated in Table II, again presented randomly against the standard sucrose solutions and to choose that sulfamate solution which gave the closest correspondence in sweetness to the standard sucrose solutions. The methodology of the tasting process for the RS determination involved (i) tasting of the sulfamate solution, (ii) rinsing the mouth with distilled water, and (iii) tasting of the standard sucrose solutions.

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