Notes

Sulfonylamine-Mediated Sulfamation of Amines. A Mild, High Yield Synthesis of Sulfamic Acid Salts

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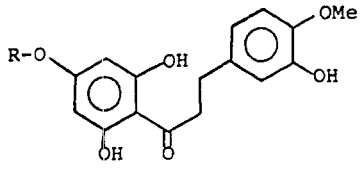
The Food and Drug Administration's 1970 banning of cyclamates for use as nonnutritive sweeteners and the more recent scrutiny to which saccharin has been subjected have caused a resurgence of activity in the development of new nonnutritive sweeteners. For several years we have been investigating the structure–activity relationship of the dihydrochalcone class of nonnutritive sweeteners[1] having general structure 1. This background of data led us to



1

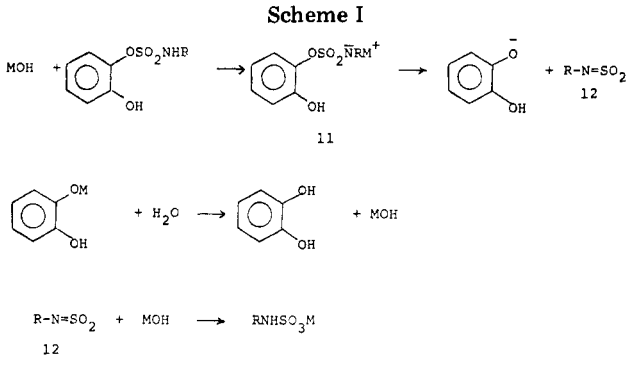
2 (R = $CH_2CH_2NH_2$)

3 (R = $CH_2CH_2NHSO_3K$)

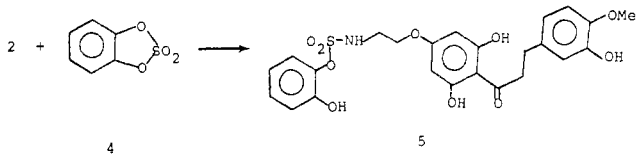
hypothesize that the sulfamic acid salt **3** should be an intensely sweet compound with a sucrose-like taste. With amine **2** available,[2] synthesis of **3** would appear a simple one-step synthesis. This very simple-in-principle and difficult-in-practice conversion represents the essence of this paper.

The methodology which has evolved for synthesis of sulfamic acids is quite limited and in practice finds application only for preparation of nonfunctionalized compounds. Known methods include (1) sulfamation of amines with chlorosulfonic acid, dioxane–SO_3, pyridine–SO_3, or trimethylamine–SO_3,[3] (2) sulfonation of isocyanates[4] or urethanes[5] with fuming sulfuric acid, and (3) sulfamation of amine hydrohalides with sulfuryl chloride–$SbCl_5$.[6] The functionality present in **2** precludes most of these methods. Treatment of **2** with trimethylamine–SO_3, the mildest of the above-mentioned reagents, gave a complex product mixture from which **3** could be isolated in only 15–20% yield by preparative high-pressure LC. Sensory analysis[7] of **3** has shown it to exhibit a strong sweet taste 352 times more intense than sucrose. The utility of **3** in food systems has been given extensive study. Clearly, a selective method of amine sulfamation is needed which is compatible with a labile functionality such as is present in **2**.

Scheme I



In an effort to understand the extraordinary hydrolytic lability of cyclic phosphate esters, Kaiser and co-workers[8] have compared the relative reactivity of catechol sulfate (**4**) and diphenyl sulfate toward hydroxide ion. The cyclic



sulfate ester was observed to hydrolyze with exclusive S–O fission at a rate more than 10^7 times that of the acyclic analogue. In view of the increased nucleophilicity afforded by amines relative to hydroxide ion,[9] it was anticipated that **2** should react with catechol sulfate to produce the aryl sulfamate **5**. In fact, reaction of **2** with **4** in DMF in the presence of triethylamine resulted in formation of **5** in quantitative yield. Further work has shown the reaction of aliphatic amines with **4**, in the presence of either excess amine or triethylamine, to be a general reaction. Results are summarized in Table I. On the other hand, the reaction of **4** with aromatic amines is quite lethargic. The reaction with primary aliphatic amines is complete within 1 h at 0 °C, whereas the reaction with aniline requires 68 h in refluxing methylene chloride for 94% consumption of **4**. This suggests that a highly selective reaction may be expected when reacting compounds bear both aliphatic and aromatic amine functionalities. During this reflux period, 28% of the desired sulfamate ester is cleaved to produce diphenylsulfamide such that the sulfamate ester is obtained in only 66% yield.

As a result of a consideration of the propensity of aryl alkanesulfonate esters to undergo sulfene-mediated hydrolysis when reacted with alkali,[10] it was anticipated that the aryl sulfamate esters prepared above would undergo

(1) DuBois, G. E.; Crosby, G. A.; Saffron, P. *Science (Washington, DC)* **1977**, *195*, 397. DuBois, G. E.; Crosby, G. A.; Stephenson, R. A.; Wingard, R. E. *J. Agric. Food Chem.* **1977**, *25*, 763.

(2) Alkylation of hesperetin (Sigma Chemical Co.) with 2-bromoethyl *N*-benzylcarbamate and potassium carbonate in DMF followed by hydrogenation with Pd/C in aqueous alkali provides **2** in 40% overall yield.

(3) Gilbert, E. E. "Sulfonation and Related Reactions"; Interscience: New York, 1965; Chapter 7 and references therein.

(4) Bieber, T. *J. Am. Chem. Soc.* **1953**, *75*, 1405.

(5) Bieber, T. *J. Am. Chem. Soc.* **1953**, *75*, 1409.

(6) Weiss, G.; Schulze, G. *Justus Liebigs Ann. Chem.* **1969**, *729*, 40.

(7) Swartz, M.; Furia, T. E. *Food Technol. (London)* **1977**, 51–55.

(8) Kaiser, E. T.; Katz, I. R.; Wulfers, T. F. *J. Am. Chem. Soc.* **1965**, *87*, 3781.

(9) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; pp 322–5 and references therein.

(10) Opitz, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 107.

(11) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1967**, *89*, 2502.

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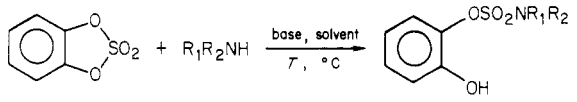
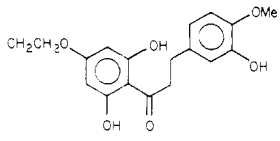
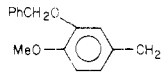
Table I. Amine Sulfamation with Catechol Sulfate

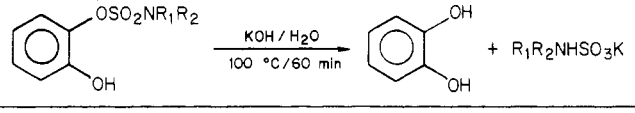


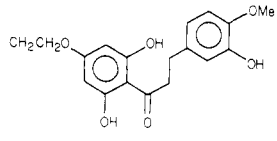
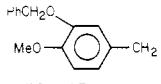
5-10

compd[13]	R_1	R_2	base	solvent	T, °C	yield, %[a]	mp, °C
5		H	Et_3N	DMF	0	77 (100)[b]	78-80
6	$PhCH_2$	H	R_1R_2NH	CH_2Cl_2	0	98	116.5-117.5
			Et_3N	CH_2Cl_2	0	89	
7	c-C_6H_{11}	H	R_1R_2NH	CH_2Cl_2	0	92	71-73
8		H	Et_3N	CH_2Cl_2	0	85	87-88
9	CH_3CH_2	CH_3CH_2	Et_3N	DMF	0	86[b]	oil
10	Ph	H	Et_3N	CH_2Cl_2	40	66	111-113

[a] Yield after recrystallization. [b] Yield after silica gel chromatography.

Table II. Hydrolysis of Aryl Sulfamates



compd[13]	R_1	R_2	yield, % HPLC[a]	yield, % isolated[b]
3		H	100	89
13	$PhCH_2$	H	94	99
14	c-C_6H_{11}	H		99
15		H	99	81
16	CH_3CH_2	CH_3CH_2		0

[a] High-pressure liquid chromatography, determined with standard solutions of 3, 13, and 15 on a Waters 30-cm, C-18 on μ-Bondapak column eluted with 0.03 M KH_2PO_4/methanol mixtures. Monitoring was done with a Schoeffel's UV detector. [b] Determined following recrystallization.

facile hydrolysis via the analogous intermediate **12** as illustrated in Scheme I. This type of heterocumulene intermediate was first reported by Burgess and co-workers, from whence the name *N*-sulfonylamine is derived. More recently, studies by Williams and Douglas[12] on the mechanism of hydrolysis of aryl *N*-methylsulfamate esters has given strong support for the proposed reaction pathway. In fact, when ester **5** was treated with 2 equiv of 1 M aqueous potassium hydroxide at reflux for 60 min, **3** was formed in quantitative yield. The sulfonylamine mechanism is supported by the fact that the N,N-disubstituted ester **9** (Table I) shows no measurable hydrolysis after 4 h under conditions where the N-monosubstituted esters are quantitatively cleaved within 1 h. Consideration of the stoichiometry of the hydrolysis reaction suggests that only 1 equiv of alkali may be required. In actuality, this is shown to be the case as exemplified by the observation that treatment of *N*-benzylsulfamate ester **6** with 1 equiv of 1 M potassium hydroxide at reflux for 1 h results in quantitative cleavage to produce only catechol and potassium *N*-benzylsulfamate. Interestingly, reaction of **6** with excess alkali results in only a trace of hydrolysis after 1 h of reflux. Clearly, the presence of a significant concentration of monoanion **11** is a prerequisite for hydrolysis. The necessity for only 1 equiv of alkali is quite fortuitous, since the highly water soluble sulfamic acid salt products can be isolated in pure form simply by removing catechol, the only other component of the crude product, by extraction. Sulfamate esters containing additional acidic groups may require more than 1 equiv of alkali, however, as illustrated by **5** where 2 equiv are necessary for facile cleavage. Results for the hydrolysis of sulfamic acid esters are summarized in Table II.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates T-60A spectrometer (60 MHz) and are recorded in parts per million from tetramethylsilane.

(12) Williams, A.; Douglas K. T. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1727.

(13) All compounds have been characterized by IR, UV, and NMR spectroscopy and exhibited satisfactory elemental analyses.

Ultraviolet spectra were recorded on a Varian Associates Cary 118 spectrophotometer. Elemental analyses were carried out by the Stanford University Microanalytical Laboratory. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

High-pressure liquid chromatography (LC) was performed on a Waters Associates system equipped with a Model 660 solvent programmer, two Model M-6000A pumps, a Schoeffel Instrument Corp. variable-wavelength ultraviolet detector, and a 30-cm, C-18 on μ-Bondapak column. Vapor-phase chromatography (VPC) was carried out on a Varian Associates Aerograph Model 920 employing a 6-ft, 5% SE-30 on Chromosorb G column. Thin-layer chromatography (TLC) was carried out on EM Laboratories precoated silica gel 60 F-254 plates (5 × 10 cm).

The diethyl ether, hexane, ethyl acetate, chloroform, and methylene chloride used were reagent grade solvents from J. T. Baker Chemical Co. Triethylamine was distilled from phosphorus pentoxide and stored over activated 4A molecular sieves. Dimethylformamide (DMF) was distilled from calcium hydride and stored over activated 4A molecular sieves. Pyridine was distilled from barium oxide and stored over activated 4A molecular sieves. Sulfuryl chloride was subjected to simple distillation prior to use.

Catechol Sulfate (4). The procedure employed is a modification of that reported by Denivelle[14] with the suggestions of Kaiser.[15]

A 55-g (0.50 mol) sample of catechol was dissolved in 79 g of pyridine and the mixture stirred vigorously with an overhead stirrer under dry argon in a 1-L, three-necked flask equipped with a thermometer and addition funnel. A 500-mL portion of hexane was then added, after which the reaction mixture was cooled to −5 °C in an ice–salt bath. A solution of 68 g (0.50 mol) of sulfuryl chloride in 100 mL of hexane was then added dropwise over 4 h while the temperature was carefully maintained between −5 and 0 °C. Stirring at 0 °C was continued overnight, after which the reaction mixture was allowed to warm to ambient temperature over 6 h. The upper layer of the two-layer reaction mixture was decanted, after which the lower layer was washed (2 × 100 mL) with ethyl acetate. The combined washes and upper layer were then washed with 5% $Cu(OAc)_2 \cdot H_2O$ until TLC (hexane–ethyl acetate, 3:1) indicated the absence of catechol (R_f 0.14). The solution was then dried over magnesium sulfate and concentrated, yielding 56.7 g of an amber liquid. TLC (hexane–ethyl acetate, 3:1) showed one component having R_f 0.40. VPC (165 °C, 60 cm^3/min He flow) showed one major component having RT = 5.0 min which was contaminated by an impurity at 7.5 min. Distillation through a 15-cm Vigreux column yielded 45.1 g (52%) of a colorless liquid, bp 76–78 °C (1.25 mm). Recrystallization from hexane yielded 38.0 g of long colorless needles, mp 35.5–36 °C (lit.[8] mp 34–35 °C).

General Procedure for Preparation of 2-Hydroxyphenyl *N*-Alkylsulfamates. A solution of 1.89 g (11.0 mmol) catechol sulfate in 2.0 mL of methylene chloride was added dropwise to a solution of 10.0 mmol of amine and 1.11 g (11.0 mmol) of triethylamine in 25 mL of DMF with vigorous stirring at 0 °C under dry argon. After 2.5 h at 0 °C, the reaction mixture was poured into 100 mL of 1% hydrochloric acid and extracted with ether (3 × 25 mL), and the combined portions were washed with water (6 × 50 mL), dried over magnesium sulfate, and concentrated, yielding the ester as a white solid, which on recrystallization from chloroform yielded an analytical sample.

2-Hydroxyphenyl *N*-[[(2,3′,6-Trihydroxy-4′-methoxydihydrochalcon-4-yl)oxy]eth-2-yl]sulfamate (5). According to the general method, 991 mg (2.85 mmol) of 2,3′,6-trihydroxy-4′-methoxy-4-(aminoethoxy)dihydrochalcone was reacted with 541 mg (3.14 mmol) of catechol sulfate in 15 mL of DMF in the presence of 318 mg (3.14 mmol) of triethylamine. Recrystallization of the crude product from chloroform yielded 1.14 g (77%) of light tan granular crystals, mp 78–80 °C. TLC (chloroform–methanol, 95:5) showed one component: R_f 0.11; IR (KBr) 2.93 (OH, NH), 6.17 (C=O) μm; UV (EtOH) 283 nm (ε 21 900); NMR (acetone-d_6) δ 2.86 (t, 2 H, J = 7 Hz, $ArCOCCH_2Ar'$), 3.36 (t, 2 H, J = 7 Hz, $ArCOCH_2CAr'$), 3.63 (t, 2 H, J = 6 Hz, CH_2N), 3.82 (s, 3 H, OCH_3), 4.14 (t, 2 H, J = 6 Hz, $ArOCH_2$), 5.97 (s, 2 H, ArH). Anal. ($C_{24}H_{25}NO_{10}S \cdot H_2O$) C, H.

General Procedure for Hydrolysis of 2-Hydroxyphenyl *N*-Alkylsulfamate. A 10-mmol sample of 1.00 M potassium hydroxide was added to 10.0 mmol of the solid sulfamate ester in a 100-mL, one-necked flask equipped with a magnetic stir bar. A 40-mL portion of distilled water was then added, and the reaction apparatus was purged with argon. The reaction mixture was then refluxed vigorously for 30 min or until TLC of an aliquot indicated the absence of starting material. The pH was adjusted to 5–6 by addition of 2% hydrochloric acid and the reaction mixture concentrated to dryness at reduced pressure. The white solid thus obtained was then extracted with boiling ether (3 × 25 mL) and dried in vacuo. Analytical samples were obtained by recrystallization from distilled water.

Potassium *N*-[[(2,3′,6-Trihydroxy-4′-methoxydihydrochalcon-4-yl)oxy]eth-2-yl]sulfamate (3). Treatment of 5.20 g (10.0 mmol) of **5** with 20.0 mmol of potassium hydroxide according to the general procedure for 60 min yielded 5.02 g of a light tan solid. High-pressure LC (10–100% MeOH in 0.03 M KH_2PO_4, linear gradient; 15-min program; flow rate 2.0 mL/min; 286 nm) showed the desired product having R_t = 12.0 min. Comparison with a standard solution of authentic material indicated a yield of 4.65 g (100%). Recrystallization from distilled water yielded 4.15 g (89%) of **3** as tiny white granular crystals: IR (KBr) 2.95 (OH), 3.03 (NH), 6.17 (C=O) μm; UV (H_2O) 282 nm (ε 20 200); NMR (Me_2SO-d_6) δ 2.97 (t, 2 H, J = 6 Hz, $ArCOCCH_2Ar'$), 3.16 (t, 2 H, J = 6 Hz, $ArCOCH_2CAr'$), 3.54 (t, 2 H, J = 5 Hz, NCH_2), 3.70 (s, 3 H, OCH_3), 4.03 (t, 2 H, J = 5 Hz, $ArOCH_2$), 5.96 (s, 2 H, ArH). Anal. ($C_{18}H_{20}KNO_9S \cdot 0.5H_2O$) C, H, N, S.

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Registry No. **2**, 74282-79-4; **3**, 70412-97-4; **4**, 4074-55-9; **5**, 74282-80-7; **6**, 74282-81-8; **7**, 74282-82-9; **8**, 74282-83-0; **9**, 74282-84-1; **10**, 74282-85-2; 2,3,6-trihydroxy-4′-methoxy-4-(2-aminoethoxy)dihydrochalcone, 74282-79-4; benzylamine, 100-46-9; cyclohexylamine, 108-91-8; 3-benzyloxy-4-methoxybenzylamine, 54170-11-5; diethylamine, 109-89-7; phenylamine, 62-53-3; potassium benzylsulfamate, 74282-86-3; potassium cyclohexylsulfamate, 7758-04-5; potassium 3-benzyloxy-4-methoxybenzylsulfamate, 74282-87-4; catechol, 120-80-9.

(14) Denivelle, L. *C. R. Hebd. Seances Acad. Sci.* **1936**, *203*, 194.
(15) Kaiser, E. T., University of Chicago, personal communication, 1978.

Amination of Aryl Sulfamate Esters. A Convenient General Synthesis of Aliphatic Sulfamides

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Recently,[1] we demonstrated that 2-hydroxyphenyl *N*-alkylsulfamate esters **1–3** could be obtained in near quantitative yields by reaction of the appropriate aliphatic amine with catechol sulfate (**4**), under very mild conditions (1 h, 0 °C).

Aromatic amines, on the other hand, being much less nucleophilic,[2] undergo a very lethargic reaction with **4**.

(1) DuBois, G. E.; Stephenson, R. *J. Org. Chem.*, preceding paper in this issue.

0022-3263/80/1945-5373$01.00/0