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Article

Identification of Isomers of Alkylaminophenylethanethiosulfuric Acids by ^{13}C-NMR Calculations Using a C-13 Chemical Shift User Database and 2D NMR Techniques

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Na obtenção de ácidos N-alquilaminoalcanotiossulfúricos, existe a possibilidade de formação de dois produtos na última etapa da síntese. No caso dos sete ácidos sintetizados neste laboratório a partir de óxido de estireno e aminas primárias alifáticas, os métodos comuns de espectroscopia não foram adequados para distinguir qual dos dois isômeros foi formado. Cálculos de deslocamentos químicos de carbono-13 empregando o programa ACD/CNMR ajudaram, mas não foram conclusivos para a identificação dos produtos. O uso de técnicas como HMQC, HMBC e TOCSY permitiu a identificação dos produtos como os ácidos 2-(N-alquilamino)-1-phenyl-1-etanotiossulfúricos.

In the synthesis of N-alkylaminoalkanethiosulfuric acids, there exists the possibility of forming two products in the last step of the synthesis. In the case of the seven acids synthesized in this laboratory from styrene oxide and primary aliphatic amines, the common spectroscopic methods were inadequate for distinguishing which of the two isomers was obtained. Carbon-13 chemical shift calculations employing the ACD/CNMR program were helpful, but not conclusive for identifying the products. The use of HMQC, HMBC and TOCSY techniques permitted the identification of the products as the 2-(N-alkylamino)-1-phenyl-1-ethanethiosulfuric acids.

Keywords: *aminoalkanethiosulfates, 2D NMR techniques, empirical calculations*

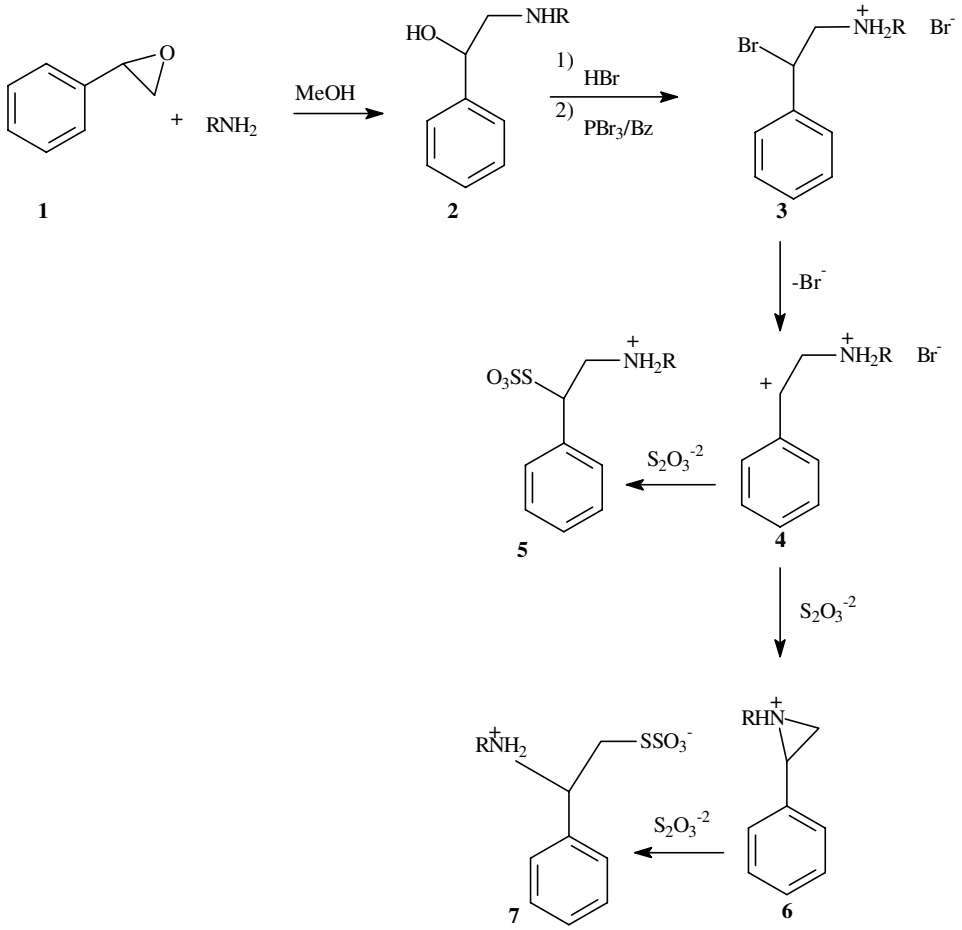
Introduction

N-Alkylaminoalkanethiosulfuric acids have demonstrated significant activity against infection by *Schistosoma mansoni* in mice and hamsters[1-4]. One of the synthetic routes for producing these compounds involves the reaction of an epoxide with a primary aliphatic amine in a modification of the Beal method (Scheme 1)[2,5,6]. The aminoalcohol is treated with hydrobromic acid, followed by phosphorous tribromide in a medium of low polarity to furnish the corresponding bromoalkanamine[7,8]. This intermediate is then converted to the N-alkylaminoalkanethiosulfuric acid (**5**) by reaction with sodium thiosulfate[9-12]. In the last step of this synthesis, there is the possibility of rearrangement via the aziridine to furnish a second product (**7**). In the case of the corresponding aliphatic compounds, the rearranged product is the predominant product[2].

The lack of data for thiosulfuric acids, especially aminothiosulfuric acids, in the consulted literature makes it difficult to estimate the chemical shifts for the carbons bound to these groups. The problem is complicated by the fact that these molecules probably exist in the zwitterionic form and computer programs, such as the ACD/CNMR program, furnish results with large degrees of error for charged molecules. For the analogous aliphatic compounds, mass spectral analysis is normally sufficient to resolve any doubts as to the isomer formed in the last step of the synthesis. In the case of the aromatic acids, however, the mass spectra were ambiguous. Seven aromatic derivatives were synthesized with different R groups (Scheme 1) and analyzed spectroscopically in an effort to confirm the structure of the products.

Material and Methods

Seven alkylaminophenylethanethiosulfuric acids were synthesized from styrene oxide and seven primary amines (propylamine, isopropylamine, butylamine, isobutylamine,



Scheme 1. Pathway for the synthesis of N-alkylaminophenylethanethiosulfuric acids. R = a) propyl; b) isopropyl; c) butyl; d) isobutyl; e) *t*-butyl; f) *sec*-butyl; g) cyclohexyl.

tert-butylamine, *sec*-butylamine and cyclohexylamine), as described elsewhere[13]. The NMR spectra were recorded in DMSO-d_6 at 100 MHz on a Bruker *AVANCE* DPX 400 spectrometer using TMS as the internal standard. Calculations of carbon-13 chemical shifts were performed using the ACD/CNMR program (Version 1.0). Six alkylaminohexanethiosulfuric acids (R = propyl, isopropyl, butyl, isobutyl, *sec*-butyl and cyclohexyl) were synthesized by a similar procedure and their carbon-13 chemical shift values were used to form a user database for re-calculation of the chemical shift values for structures **5** and **7** (Scheme 1), as well as their uncharged forms (**8** and **9**). The syntheses and properties of these six compounds (**10**) will be published in the near future.

HMQC: r. t., DMSO-d_6, Number of Scans (NS) = 32, aquisition time (AQ) = 0.127 s, relaxation delay (d_1) = 2 s, evolution delay (d_2) = 3.44 ms, 90° pulse, 11.3 µs for ^{1}H, 12 µs for ^{13}C hard pulses and 72 µs for ^{13}C GARP decoupling; 1024 data points in F_2, 512 increments in F_1; spectral width 12 ppm in F_2 and 158 ppm in F_1; apodization with sine-bell squared in F_2 and sine-bell in F_1 prior to double Fourier transformation.

HMBC: r. t., DMSO-d_6, NS = 16; AQ = 0.449 s; d_1 = 2 s; d_2 = 3.45 ms; delay for evolution of long range coupling (d_6) = 60 ms; 1024 data points in F_2 and 382 increments in F_1; spectral width 11.4 ppm in F_2 and 221.3 ppm in F_1; apodization with sine-bell squared in F_2 and sine-bell in F_1 prior to double Fourier transformation.

TOCSY: r. t., DMSO-d_6, NS = 8; AQ = 0.246 s; d_1 = 2 s; 90° pulse, 7.2 µs for ^{1}H; 3 dB attenuation of the 90° pulse and 15 dB attenuation of the spin lock pulse; TRIM pulse = 2.5 msec, mixing time = 30 ms; 60° pulse of 23.3 µs; spectral width of 11.24 ppm in both dimensions; 128 experiments in F_1.

Results and Discussion

Initial ACD calculations of the expected carbon-13 chemical shift values resulted in large confidence limits for the methine and methylene carbons bound to the thiosulfate and ammonium groups for both isomers **5** and **7**, thus preventing the assignment of the signals to these carbons

with confidence. There are four possible molecular forms which must be considered in the calculation of the theoretical chemical shift values: the two isomers in the zwitterionic (**5** and **7**) and undissociated (**8** and **9**) forms. Although the zwitterionic form would be expected to occur in aqueous medium, the undissociated form may predominate in an organic solvent, as occurs with the common aminoacids. The results of the calculations for these four forms are given in Table 1. The values for the aromatic carbons are not shown since there was not much variation in their values. The numbering of the carbons corresponds to the structures shown in Fig. 1.

The results of calculation of the ^{13}C chemical shift values for **5** and **8** using the ACD/CNMR program are as follows. Those for the methylene carbon of the uncharged form varied from δ 57 to 60 (confidence limits = 1.8 to 5.1).

Table 1. ^{13}C-NMR chemical shifts for the charged (**5** and **7**) and uncharged (**8** and **9**) forms of the two possible isomers (**5** and **7**) of seven N-alkylaminophenylethanethiosulfuric acids calculated using the ACD/CNMR program without correction based on a user database (See Fig. 1 for assignment of the carbon atom number).

Compound	C1	C2	C1'	C2'[a]	C3'[a]	C4'
	δ	δ	δ	δ	δ	δ
Structure **8**						
8a	60.22±2.0	54.27±3.6	51.97±0.7	23.89±1.1	12.89±0.5	
8b	58.63±3.5	52.29±1.6	50.82±2.7	22.90±0.1		
8c	60.40±1.8	50.83±0.1	49.14±1.9	32.94±1.7	20.90±0.5	14.20±0.5
8d	60.36±1.8	51.24±0.5	57.99±0.8	28.66±0.7	20.90±0.2	
8e	57.07±5.1	53.24±2.5	51.81±6.7	29.28±1.6		
8f	58.66±3.5	55.79±5.1	55.66±1.1	29.90±0.6	10.05±0.3	20.33±1.5[b]
8g	58.92±3.3	52.67±2.0	57.58±1.2	31.75±0.8	25.11±1.4	25.72±1.3
Structure **5**						
5a	58.10±11.3	50.12±14.0	50.07±5.8	20.22±5.2	11.70±0.8	
5b	56.48±11.3	48.14±13.2	52.66±1.9	21.20±4.5		
5c	58.24±11.4	46.68±15.5	48.27±5.4	28.72±5.3	20.30±0.1	14.20±0.5
5d	58.19±11.4	47.09±14.0	55.94±7.2	26.77±3.6	20.60±0.1	
5e	54.58±11.3	49.09±13.4	57.61±0.3	26.00±7.3		
5f	56.52±11.3	51.64±15.0	56.58±3.7	26.70±5.2	10.20±0.4	15.69±4.5[b]
5g	56.86±11.3	48.52±13.3	59.06±2.4	29.00±6.0	25.00±0.7	25.70±1.3
Structure **9**						
9a	47.43±3.5	54.51±9.9	49.07±0.8	23.46±2.3	11.93±1.3	
9b	45.36±3.9	52.58±6.7	47.71±3.3	23.07±0.2		
9c	45.37±3.9	57.51±8.1	46.86±0.5	33.80±1.2	20.30±0.4	14.20±0.5
9d	43.50±3.7	54.90±9.9	56.25±4.3	29.80±0.5	20.90±0.2	
9e	45.51±3.9	51.14±7.9	53.61±3.3	29.46±1.6		
9f	48.02±3.1	52.95±8.9	53.35±2.1	31.86±0.3	10.05±0.3	20.56±1.4[b]
9g	45.36±3.9	54.22±9.9	57.66±4.0	35.35± -	25.11±1.4	25.72±1.3
Structure **7**						
7a	45.10±5.8	50.27±29.8	47.01±6.3	22.18±6.1	11.70±0.8	
7b	43.58±4.4	41.21±29.9	50.46±5.2	19.36±6.3		
7c	43.59±4.4	51.77±27.5	44.06±7.0	29.28±7.6	20.30±0.1	14.20±0.5
7d	41.71±2.7	50.66±29.8	53.89±5.1	27.98±4.2	20.60±0.1	
7e	43.35±5.1	40.15±29.5	60.97± -	26.56±7.0		
7f	45.24±6.0	41.44±30.0	56.49±3.7	28.24±6.7	10.20±0.4	16.19±4.7[b]
7g	45.36±3.9	56.84±8.6	57.66±4.0	35.35± -	25.11±1.4	25.72±1.4

[a]The equivalent carbons on the cyclohexyl ring have identical chemical shifts.
[b]These values refer to carbon 2" in the N-alkyl group (Fig. 1).

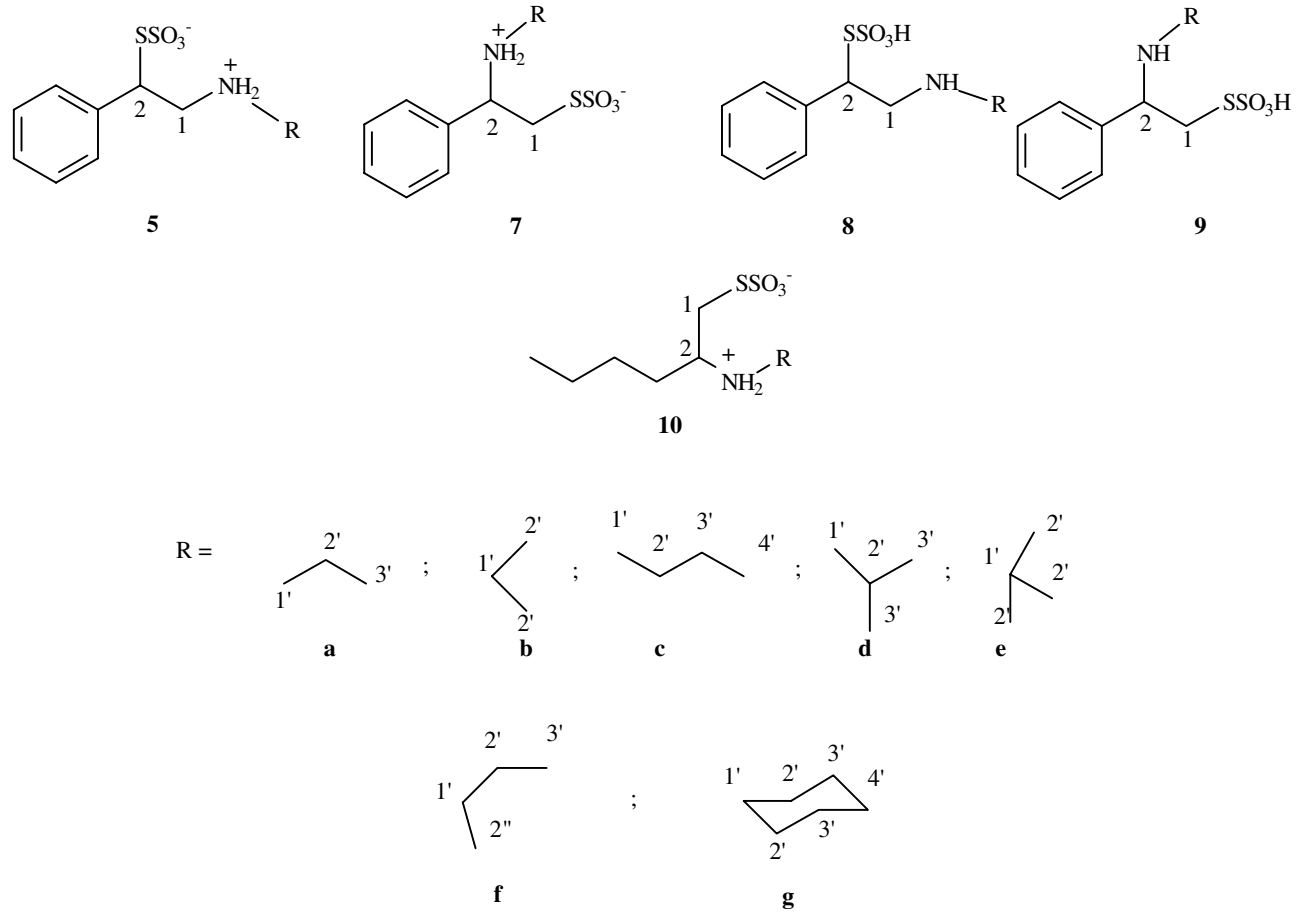


Figure 1. Structures and carbon numbering system used in Tables 1 to 5.

Those for the same carbon of the zwitterionic form were calculated to range from δ 55 to 58 (confidence limits = 11.3 to 11.4). The calculated values for the methine carbon bound to the undissociated thiosulfuric acid group varied from δ 51 to 56 (confidence limits = 0.5 to 5.1). Those for the thiosulfate varied from δ 47 to 52 (confidence limits = 13.3 to 15). Again, there is a small decrease in the values for the charged forms. However, because of the large increase in the confidence limits for the dissociated forms, this difference becomes insignificant. In this case, there is a large increase in the calculated values for both carbons.

The delta values calculated for **7** and **9** were as follows. The calculated values for the methylene carbon attached to the undissociated thiosulfuric acid group varied from δ 43 to 48 (confidence limits = 3.1 to 3.9) and for the methine carbon carrying the amino group varied from δ 51 to 58 (confidence limits = 6.7 to 9.9). The δ values calculated for the same methylene bound to the dissociated primary thiosulfate group in **7** varied from δ 42 to 45 (confidence limits = 2.7 to 6.0) and for the methine carbon bound to the ammonium group varied from δ 40 to 51 (confidence limits = 27.5 to 30). Thus, the calculated values for the methylene carbon in **7** were slightly lower than for **9**, but of the same order of magnitude. The calculated chemical shift values for the methine carbons bound to the ammonium groups were generally smaller than those for the same carbons bound to the amino group. However, the confidence limits increased so much that any difference in calculated delta values became insignificant.

A user database with the known values obtained from the ^{13}C-NMR spectra of six 2-(alkylamino)-1-hexanethiosulfuric acids was created (Table 2). As a result, new chemical shift values could be calculated with greater precision.

The ^{13}C-NMR spectra of the N-alkylaminohexanethiosulfuric acids were determined in the same solvent (DMSO-d_6) as the N-alkylaminophenylethanethiosulfuric acids. Thus, there should be no difference in the degree of dissociation of the two series of compounds. As a basis for calculating the corrected chemical shift values for the uncharged forms of the aromatic acids, the aminohexanethio-

Table 2. Observed experimental ^{13}C-NMR chemical shift values for the carbons of six 2-(alkylamino)-1-hexanethiosulfuric acids (**10**) (See Fig. 1 for specification of the carbon atom number).

Compound	C-1	C-2	C-1'	C-2'[a]	C-3'[a]	C-4'
R	δ	δ	δ	δ	δ	δ
Propyl	33.93	57.74	46.42	19.09	10.78	
Isopropyl	34.49	55.10	48.18	18.88		
Butyl	33.91	57.77	44.63	27.57	19.13	13.38
Isobutyl	34.08	58.81	51.90	25.60	19.84	
Sec-butyl	34.90	53.38	55.66	26.70	9.53	15.50[a]
Cyclohexyl[b]	34.69	55.04	54.52	28.72	23.75	24.62

[a]The equivalent carbons on the cyclohexyl ring have identical chemical shifts. [b]These values refer to carbon 2" in the N-alkyl group (Fig. 1).

Table 3. ^{13}C-NMR chemical shifts for the charged (**5** and **7**) and uncharged (**8** and **9**) forms of the two possible isomers (**5** and **7**) of seven N-alkylaminophenylethanethiosulfuric acids calculated using the ACD/CNMR program with a user database (See Fig. 1 for assignment of the carbon atom number)[a].

Compound	C-1	C-2	C-1'	C-2'[b]	C-3'[b]	C-4'
	δ	δ	δ	δ	δ	δ
Structure **8**						
8a	60.22±2.0	54.27±3.6	51.97±0.7	23.89±1.1	12.89±0.5	
8b	58.63±3.5	52.29±1.6	50.82±2.7	22.90±0.1		
8c	60.40±1.8	50.83±0.1	49.14±1.9	32.94±1.7	20.90±0.5	14.20±0.5
8d	60.36±1.8	51.24±0.5	53.81±0.3	25.10±0.3	19.84± -	
8e	57.07±5.1	53.24±2.5	51.81±6.7	29.28±1.6		
8f	58.66±3.5	55.79±5.1	57.79±2.3	24.79±1.3	9.53± -	15.14±1.1[c]
8g	58.92±3.3	52.67±2.0	56.65±2.3	26.61±1.3	23.75± -	24.62± -
Structure **5**						
5a	58.10±11.3	46.86±1.9	48.32±0.3	17.18±1.3	10.78± -	
5b	56.48±11.3	44.88± --	50.31±2.3	18.52±1.1		
5c	58.24±11.4	43,42±1.5	46.54±0.3	25.66±1.3	19.13± -	13.38± -
5d	58.19±11.4	43.83±1.1	53.81±0.3	25.10±0.3	19.84± -	
5e	54.55±11.4	45.82±0.9	54.58±1.2	26.39±0.6		
5f	56.52±11.3	49.80±6.1	57.79±2.3	24.79±1.3	9.53± -	15.14±1.1[c]
5g	56.86±11.3	45.25±0.3	56.65±2.3	26.81±1.3	23.75± -	24.62± -
Structure **9**						
9a	38.27±1.4	56.02±1.7	46.28±0.3	18.68±0.3	10.78± -	
9b	38.83±1.4	53.38±1.7	50.22±0.4	18.72±0.2		
9c	38.84±1.7	56.05±1.7	44.49±0.3	27.16±0.3	19.13± -	13.38± -
9d	36.96±2.1	57.09±1.7	51.76±0.3	26.05±0.4	19.84± -	
9e	38.97±1.5	52.32±2.0	55.85±5.5	26.60±0.7		
9f	38.41±1.4	51.66±1.7	57.70±2.3	26.29±0.3	9.53± -	15.64±0.2[c]
9g	38.83±1.4	53.32±1.7	56.56±0.5	28.31±0.3	23.75± -	24.62± -
Structure **7**						
7a	38.27±1.4	56.02±1.7	46.28±0.3	18.68±0.3	10.78± -	
7b	38.83±1.4	53.38±1.7	50.22±0.4	19.02±0.2		
7c	38.84±1.7	56.05±1.7	44.49±0.3	27.16±0.3	19.13± -	13.38± -
7d	36.96±2.1	57.09±1.7	51.76±0.3	26.05±0.4	19.84± -	
7e	38.97±1.5	52.32±2.0	55.85±5.5	26.90±0.7		
7f	38.41±1.4	51.66±1.7	57.70±0.4	26.29±0.3	9.53± -	15.64±0.2[c]
7g	38.83±1.4	53.32±1.7	56.56±0.5	28.31±0.3	23.75± -	24.62± -

[a]No values were provided by the program for the confidence limits with dashes. [b]The equivalent carbons on the cyclohexyl ring have identical chemical shifts. [c]These values refer to carbon 2" of the N-alkyl group (Fig. 1).

sulfuric acids were also considered to be in the undissociated form, whereas, for the dissociated species of the aromatic thiosulfuric acids, the aliphatic acids were considered to be in the corresponding zwitterionic form. The results of the calculations based on the C-13 chemical shift database are shown in Table 3.

In the calculations of the ^{13}C chemical shift values for the uncharged structure **8** based on the user database which included the values for the aminohexanethiosulfuric acids, there were no significant changes in the values or in the confidence limits calculated for the methylene and methine carbons. For the charged structure **5**, a decrease in the chemical shift values for the methine carbon (C-2) was observed with a large decrease in the confidence limits. However, there were no changes in the chemical shift values for the methylene carbons (C-1) and no improvement in the corresponding confidence limits. This observation may be due to the fact that these isomers bear the thiosulfate group on C-2 and the ammonium group on C-1, whereas, the user database was based on isomers in which these groups are inverted.

In the calculations of the ^{13}C chemical shift values for the corresponding methylene carbons (C-1) of structures **7** and **9** after inclusion of the user database, the delta values

Table 4. The observed ^{13}C-NMR chemical shift values for the product **5** with their proposed assignments (See Fig. 1 for specification of the carbon atom number).

Compound	C	*o*-C	*m*-C	*p*-C	C-1	C-2	C-1'	C-2'[a]	C-3'[a]	C-4'
	δ	δ	δ	δ	δ	δ	δ	δ	δ	δ
Propyl	138.4	128.0	127.6	129.0	52.2	48.6	49.1	18.9	10.8	
Isopropyl	138.3	128.9	127.9	128.4	50.5	46.6	48.8	18.5		
Butyl	138.4	128.0	127.6	128.9	52.2	48.6	47.2	27.3	19.1	13.4
Isobutyl	138.6	128.0	127.5	130.0	53.2	48.6	54.5	25.3	19.8.	
t-Butyl	138.2	129.0	127.7	128.1	47.0	49.5	57.1	25.1.		
s-Butyl	138.4	128.1	127.6	129.0	49.9	49.0	55.7	25.2	9.5	15.3[b]
Cyclohexyl	138.4	128.9	127.6	28.0	49.6	49.0	56.8	28.5	24.7	23.8

[a]The equivalent carbons on the cyclohexyl ring have identical chemical shifts. [b]These values refer to carbon 2" in the N-alkyl group (Fig. 1).

Table 5. ^{13}C-NMR (100 MHz) data for the some of the N-alkylaminophenylethanethiosulfuric acids obtained via the HMQC [^{1}J(C,H)], TOCSY and HMBC [^{n}J (C,H), n = 2 and 3] experiments.

		HMQC	HMBC		TOCSY
	δ_C	δ_H	^{2}J(C, H)(δ)	^{3}J(C, H)	^{1}H(δ) X ^{1}H(δ)
Propyl (**5a**)					
C-1	52.2	3.75	H-2(4.65)		H-1(3.54), H-2(4.63)
		3.54			H-1(3.75), H-2(4.63)
C-2	48.6	4.63	H-1(3.54, 3.75)		H-1 (3.45, 3.75)
C-1'	49.1	2.88	H-2'(1.60)	H-3'(0.88)	H-2'(1.60), H-3(0.88)
C-2'	18.9	1.60	H-3'(0.88)		H-1'(2.88), H-3(0.88)
			H-1'(2.88)		
C-3'	10.8	0.88	H-2'(1.60)	H-1'(2.88)	H-2'(1.60), H-3(0.88)
Ar-1	138.4		H-2(4.63)	H-1(3.54, 3.75)	
Ar-2	128.0			H-2(4.63)	
Butyl (**5c**)					
C-1	52.19	3.77	H-2(4.64)		
		3.56			
C-2	48.53	4.64	H-1(3.56	3.77)	
C-1'	47.21	2.93	H-2'(1.55)	H-3'(1.31)	
C-2'	27.28	1.55		H-4'(0.87)	
C-3'	19.10	1.31	H-4'(0.87)		
C-4'	13.39	0.87	H-3'(1.31)	H-2'(1.55)	
Ar-1	138.5		H-2(1.55)		
Ar-2	128.0			H-3(1.31)	

Table 5. (cont.)

Isobutyl (**5d**)					
C-1	53.2	3.53	H-2(4.70)		
C-2	48.6	4.70			
C-1'	54.5	2.82	H-2'(1.96)	H-3'(0.96)	
C-2'	25.3	1.96	H-3'(0.96)		
C-3'	19.8	0.96	H-2'(1.96)	H-3'(0.96)	
Ar-1	138.6		H-2(1.96)		
Ar-2	128.0			H-2(1.96)	
t-Butyl (**5e**)					
C-1	47.0	3.83	H-2(4.57)		H-1(3.50), H-2(4.57)
		3.50			H-1(3.83), H-2(4.57)
C-2	49.5	4.57	H-1(3.50, 3.83)		H-1(3.50), H-1(3.83)
C-1'	57.1	-	H-2'(1.30)	H-1(3.83weak)	
C-2'	25.1	1.30		H-2'(1.30)	
Ar-1	138.2		H-2(4.57)		
Ar-2	129.0	7.37		H-2(4.57)	
sec-Butyl (**5f**)					
C-1	49.9	3.78	H-2(4.63)		
		3.58			
C-2	49.0	4.63	H-1(3.53, 3.78)		
C-1	55.7		H-2'(1.47)	H-3'(0.89)	
			H-2"(1.20)		
C-2'	25.2	1.74	H-3'(0.89)	H-2''(1.20)	
		1.47			
C-2"	15.3	1.20		H-2'(1.47, 1.74)	
C-3'	9.5	0.89	H-2'(1.47, 1.74)		
Ar-1	138.4		H-2(4.63)	H-1(3.78)	
Ar-2	128.1			H-2(4.63)	
Cyclohexyl (**5g**)					
C-1	49.6	3.80	H-2(4.62)		
		3.60			
C-2	49.0	4.62	H-1(3.60, 3.80)		
C-1'	56.8	3.05	H-2'(1.73, 2.01)	H-2(4.62 weak)	
				H-3'(1.27, 1.57)	
C-2'	28.5	2.01(eq)	H-1'(3.05)		
		1.73(ax)	H-3'(1.27, 1.57)		
C-3'	24.7	1.57(eq)	H-2'(2.01, 1.73)	H-1'(3.05)	
		1.27(ax)			
C-4'	23.8	1.13	H-3'(1.27	1.57)	
Ar-1	138.4		H-2(49.0)	H-1(49.6)	
Ar-2	128.9			H-2(49.0)	

obtained were much lower than those obtained without correction. There was also a significant decrease in the confidence limits. There was little change in the chemical shift values calculated for the methine carbon (C-2) bound to the thiosulfuric acid group in the uncharged form **9**, although the confidence limits decreased significantly. For the zwitterionic form, there was an increase in the chemical shift values relative to those obtained without use of the user database and a large improvement in the confidence limits.

Based on these data and the results of the calculations shown in Table 3, structures **7** and **9** could be excluded as

probable structures for the products obtained in these syntheses. The DEPT experiment could distinguish between methylene and methine carbons. The structure for which the calculated values most closely approached the observed values was **5**. However, because of the proximity of the experimental values observed for carbons C-1, C-2 and C-1' (Table 4) and the large confidence limits for the chemical shift values calculated for C-1 of structure **5** (Table 3), there was still doubt as to the assignments of the signals to these three carbons. Therefore, it was necessary to resort to 2D NMR techniques to assign these signals with confidence and to confirm the results of the calculations. The use of other spectral techniques was of no help in this case. Infrared spectroscopy, of course, would be of no assistance in distinguishing between isomers. In the case of the corresponding aliphatic compounds, mass spectral analysis easily permitted the differentiation of the isomers[2]. In the present case, however, the mass spectra were ambiguous and did not permit a firm assignment of the structures[13]. Therefore, the HMBC, HMQC and TOCSY experiments were performed to verify which groups were bound to the methylene and methine carbons. The results of these experiments are shown in Table 5. The values for **5b** are not shown since, in this case, a mixture of products was obtained. The HMQC and HMBC experiments established the assignments of the signals to the respective carbons and the TOCSY experiment confirmed the results.

Conclusions

The results from the ACD/CNMR calculations using a user database were helpful, but were not conclusive because of the existence of charges on the molecules and the lack of data in the literature consulted for aminoalkanethiosulfuric acids. However, the use of HMQC, HMBC and TOCSY experiments established that, in this series of aromatic compounds, the principal product is that in which the thiosulfate group is bound to the benzilic carbon. In DMSO-d_6 the zwitterionic form is preferred. In general, no or very weak long-range coupling was observed through the ammonium group.

The $\Delta\delta$ contribution for the thiosulfate group bound to the terminal methylene carbon was established as approximately 16.5 ppm. From the results obtained in these experiments, the $\Delta\delta$ for this group bound to the methine carbon could then be estimated as 9.4 ppm.

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