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STEREOCHEMISTRY OF ORGANIC SULFUR COMPOUNDS. PART 15[1]. THE IMPORTANT ROLE OF PROTONATION IN THE INVESTIGATION OF THE INTERACTIONS BETWEEN THE THIOETHER AND SOME AMINE FUNCTIONS IN 1,2-DISUBSTITUTED PHENYLETHANES.

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SUMMARY: Syntheses and conformational study of 1-X-2-phenylethyl methyl sulfide (X=NH_2, NHMe, NMe_2 and $^+NMe_3$) are reported. Conformational populations have been inferred mainly from the variations in vicinal coupling constants induced by protonation and solvent polarity changes. Steric factors are in general dominant. The dimethylamino group additionally showed a strong repulsive gauche effect. However, when the nitrogen bore positive charge, the attractive ^+N/SMe interaction dominated the equilibria except in the trimethylammonium derivative. Solvent polarity effects were very significant.

INTRODUCTION

The nature of the interactions between certain sulfur and oxygen functions in several β-oxygenated thioderivatives has previously been the object of our attention[2]. The previous studies revealed the importance of polar factors in controlling conformational equilibria. Recently, we have extended these studies to thioderivatives bearing other heteroatomic functions on the adjacent carbon. Along these lines, the study of β-nitrogenated sulfur derivatives may be interesting in view of the increasing amount of medical and biological compounds bearing the N-C-C-S fragment[3]. In addition, the preceding study of 2-thioderivatives of N-phenyl-1-phenylethylamine[4] indicated that sulfur compounds with a neighboring amine group are preferred models for the evaluation of polar interactions because aminic nitrogen was easily protonated and its electronic availability thereby modified. This introduced large shifts in equilibrium that served as a very good tool for analyzing the various interactions in these systems.

In this paper the synthesis and conformational analysis of 1-phenyl-2-

methylthioethylamine (**1**) and some of its derivatives are reported (see Scheme 1). The variation in size and charge of the different functions to be studied is devoted to give information on the influence of these factors on the not very well known N-C-C-S interaction. The conclusions obtained in this work will provide the foundations for the future study of more complex β-nitrogenated sulfur compounds.

1: A= NH_2, B= SMe **1°**: A= $X^{-+}NH_3$, B= SMe

2: A= NHMe, B= SMe **2°**: A= $X^{-+}NH_2Me$, B= SMe

3: A= NMe_2, B= SMe **3°**: A= $X^{-+}NHMe_2$, B= SMe

Ph-CH(A)-CH_2(B)

4: A= $I^{-+}NMe_3$, B= SMe

5: A= NH_2, B= $TsO^{-+}SMe_2$

(X^-= picrate ion)

Scheme 1

RESULTS AND DISCUSSION

Synthesis

The treatment of 2-chloro-2-phenylethyl methyl sulfide with aqueous ammonia, methylamine or dimethylamine yielded the thioethers **1**, **2** and **3**, respectively. The reaction of **3** with methyl iodide led to the ammonium salt **4** and the treatment of **1** with methyl p-toluensulfonate afforded the sulfonium salt **5**.

The substitution of chlorine by the amine group had to be carried out immediately after the preparation of the chloro derivative because this chlorothioether at room temperature (in ca 300 h, monitored by ^{1}H-nmr) equilibrated with a minor amount of another compound, whose ^{1}H-nmr signals were compatible with the structure of the regioisomer, 2-chloro-1-phenylethyl methyl sulfide. On the other hand, the starting material, 2-chloro-2-phenylethyl methyl sulfide, could be obtained from either regioisomeric alcohol, 1-phenyl-2-methylthioethanol and 2-phenyl-2-methylthioethanol, by treatment with hydrogen chloride or thionyl chloride. All these results suggested that the methylsulfenyl group participates in the departure of the OH or Cl groups in the β-position.

Conformational Analysis

General Considerations

The analysis of the ^{1}H-nmr spectra of the compounds studied in this work, recorded in different conditions, yield the chemical shifts and coupling

constants listed in Tables 1 to 4. The populations of the three staggered rotamers in equilibrium (Figure 1) were obtained as previously described[5], using model coupling constants calculated by Altona's equation[6,7].

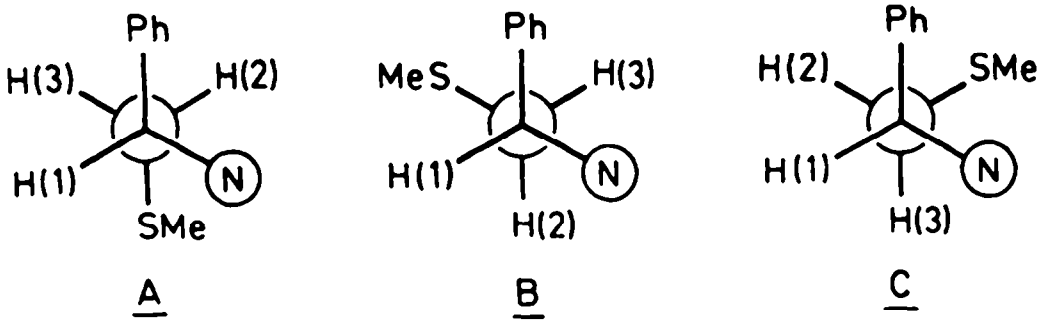


Figure 1.- Staggered rotamers around the C(1)-C(2) bond.

The evaluation of populations has two mathematically possible solutions that correspond to the uncertainty of assigning H(2) and H(3) to the observed chemical shifts [δH(i) and δH(j) in Tables 1-4). Since $\Delta\delta$ between these two protons was in general very small, chemical shifts could not be used as an assignment criterion. The nonexistence of additional data (i.e. long range couplings[2]) that would clearly point to one of the two solutions, made it necessary to turn to other methods. The qualitative prediction of the conformational populations from a careful study of the existing interactions in each rotamer, allowed a tentative proton assignment to be made. In some favorable cases, lanthanide shift reagents (LSR) served to check the assignment. To confirm the assignment, a comparative study of the various compounds will be presented and the influence of controlled medium changes (acidity to induce protonation, and solvent polarity) on conformational equilibria will be evaluated. These data can then be used to confirm the correctness of the different arguments applied in the a priori conformational analysis made for proton assignment.

To achieve protonation, all compounds (except 4) were studied in trifluoracetic acid (TFA), inasmuch as this solvent transforms NR_2 into $^{+}NHR_2$ (as demonstrated by the appareance of a new vicinal coupling CH-N$\underline{H}R_2$ in the ^{1}H-nmr spectra), leaving the sulfur group unaltered[4]. The changes in equilibria in progressing from $CDCl_3$ to pure TFA were studied in detail, by means of numerous intermediate samples containing increasing TFA:substrate molar ratios, so as to correlate the conformational preferences observed in both pure solvents.

Table 1.- ^{1}H-NMR parameters of compounds **1** to **4** in $CDCl_3$ and DMSO-$\underline{d}_6$

Comp	Solv	Conc[a]	Chem.shifts(ppm) H(1)	H(i)	H(j)	Me-S	Me-N	Coup.const.(Hz) $J_{1,i}$	$J_{1,j}$	$J_{i,j}$
1	$CDCl_3$	20	4.06	2.63	2.77	2.04	-	9.2	4.2	-13.3
1	"	10	4.09	2.65	2.80	2.06	-	9.3	4.1	-13.4
1	"	5	4.10	2.66	2.81	2.08	-	9.0	4.3	-13.2
1	"	2.5	4.11	2.67	2.81	2.08	-	9.1	4.2	-13.3
1	"	1.3	4.12	2.67	2.82	2.09	-	9.1	4.2	-13.3
1	(8:1)[b]	5	4.10	2.66	2.80	2.07	-	9.1	4.3	-13.3
1	(4:1)[b]	5	4.09	2.65	2.78	2.06	-	8.9	4.4	-13.3
1	(2:1)[b]	5	4.07	2.63	2.76	2.05	-	8.8	4.5	-13.3
1	(1:1)[b]	5	4.06	2.63	2.74	2.04	-	8.8	4.6	-13.3
1	DMSO-$\underline{d}_6$	5	3.96	2.62	2.69	1.99	-	8.1	5.3	-13.1
2	$CDCl_3$	10	3.62	2.70	2.77	2.07	2.30	9.0	4.6	-13.4
2	"	5	3.63	2.70	2.78	2.07	2.30	9.1	4.5	-13.4
2	"	2.5	3.63	2.71	2.78	2.08	2.31	9.1	4.6	-13.4
2	"	1.3	3.63	2.71	2.78	2.08	2.31	9.4	4.5	-13.4
2	(8:1)[b]	3	3.63	2.69	2.76	2.07	2.30	9.3	4.5	-12.9
2	(4:1)[b]	3	3.62	2.68	2.75	2.06	2.28	8.9	4.8	-13.4
2	(2:1)[b]	3	3.61	2.67	2.73	2.05	2.26	9.0	4.8	-13.4
2	(1:1)[b]	3	3.61	2.66	2.72	2.04	2.25	8.8	4.8	-13.0
2	DMSO-$\underline{d}_6$	5	3.69	2.77	2.71	1.98	2.17	7.4	6.5	-13.4
3	$CDCl_3$	10	3.52	3.10	2.91	1.97	2.24	5.5	8.6	-12.9
3	DMSO-$\underline{d}_6$	4.5	3.62	3.06	2.91	1.94	2.15	5.5	8.9	-12.9
4	$CDCl_3$	1	5.39	3.51	3.33	2.21	3.48	4.0	11.6	-13.1
4	(10:1)[b]	2.5	5.35	3.46	3.39	2.17	3.28	3.7	11.8	-13.2
4	(4:1)[b,c]	2.5	5.17	3.45	3.41	2.11	3.26	4.6	10.6	-13.2

[a] % in w/v. [b] $CDCl_3$:DMSO-$\underline{d}_6$ ratio in v/v. [c] At higher $CDCl_3$:DMSO-$\underline{d}_6$ ratios and in pure DMSO-$\underline{d}_6$ the spectra resulted deceptively simple.

Table 2.- ^{1}H-NMR parameters of compounds **1** to **3** in $CDCl_3$ (in the presence of TFA) and TFA.

			Chem.shifts(ppm)					Coup.const.(Hz)		
Comp	Solv[a]	Conc[b]	H(1)	H(i)	H(j)	Me-S	Me-N	$J_{1,i}$	$J_{1,j}$	$J_{i,j}$
1	0.2	1.8	4.13	2.75	2.84	2.06	-	9.0	4.5	-13.7
1	0.4	1.8	4.14	2.84[c]		2.04	-	-	-	-
1	0.8	1.7	4.19	2.98	2.90	2.00	-	8.1	6.7	-14.1
1	1.0	1.6	4.22	3.01	2.91	1.99	-	8.0	6.5	-14.3
1	1.4	1.5	4.28	3.03	2.94	2.04	-	9.1	5.7	-14.5
1	2.4	1.3	4.40	3.07	3.01	2.11	-	10.7	4.1	-14.7
1	(12:1)	2.1	4.49	3.12	3.09	2.18	-	10.3	4.8	-14.9
1	(4:1)	2.1	4.52	3.15	3.11	2.18	-	10.3	4.5	-14.8
1	TFA	4.6	4.63	3.26	3.21	2.21	-	10.7	3.8	-15.0
2	0.2	3.6	3.71	2.79	2.82	2.04	-	8.0	5.7	-13.4
2	0.3	3.4	3.81	2.88[c]		2.05	-	-	-	-
2	0.5	3.1	3.89	2.99	2.92	2.05	-	7.7	6.5	-13.7
2	0.6	2.9	3.98	3.09	2.96	2.05	-	7.0	7.2	-13.6
2	0.8	2.6	4.08	3.18	3.01	2.06	-	6.4	8.0	-13.8
2	1.2	2.4	4.15	3.22	3.03	2.06	-	6.5	8.2	-13.9
2	1.6	2.1	4.17	3.21	3.04	2.06	-	7.2	7.4	-14.1
2	2.8	2.8	4.21	3.17	3.06	2.07	-	8.3	6.2	-14.4
2	5.0	2.4	4.24	3.15	3.07	2.06	-	9.3	5.2	-14.6
2	(4:1)	4.8	4.25	3.16	3.09	2.08	-	9.9	4.7	-14.7
2	TFA	4.8	4.42	3.31	3.23	2.10	2.66[d]	10.3	4.6	-14.7
3	0.2	3.9	3.68	3.13	2.98	1.97	2.32	5.4	9.1	-12.9
3	0.5	3.7	3.90	3.20	3.07	1.98	2.46	4.8	9.8	-12.9
3	0.7	3.5	4.12	3.27	3.16	1.98	2.58	4.1	10.7	-13.1
3	1.0	3.3	4.29	3.32	3.24	1.98	2.70	3.8	11.2	-13.3
3	1.2	3.1	4.33	3.30	3.23	1.98	2.72	3.7	11.5	-13.6
3	1.4	2.8	4.36	3.29	3.22	1.98	2.70/2.78	4.6	10.6	-13.4
3	2.0	2.7	4.44	3.26	3.21	2.01	2.70/2.82	5.2	9.8	-13.7
3	3.1	2.3	4.51	3.25	3.19	2.04	2.73/2.83	6.3	9.1	-14.1
3	5.1	1.7	4.51	3.25	3.18	2.07	2.74/2.85	7.6	7.7	-14.1
3	6.7	5.2	4.48	3.25	3.15	2.08	2.73/2.85	8.0	7.5	-14.3
3	(9:1)	6.5	4.44	3.25	3.13	2.08	2.71/2.86	8.5	7.1	-14.3
3	(4:1)	6.5	4.43	3.29	3.15	2.12	2.74/2.90	9.4	6.3	-14.5
3	TFA	6.5	4.46	3.35	3.15	2.23	2.84/3.05[e]	10.2	5.4	-15.1

[a] Solvent is $CDCl_3$ unless otherwise stated; the numbers indicate the TFA:substrate molar ratio and, when in parenthesis, the relation $CDCl_3$:TFA in v/v. [b] % in w/v. [c] Deceptively simple spectra. [d] Triplet. [e] Two doublets.

Table 3.- ^{1}H-NMR parameters of picrates **1**° to **3**° in $CDCl_3$, DMSO-$\underline{d}_6$ and TFA and in several mixtures of these solvents.

Comp	Solv	Conc[a]	Chem.shifts(ppm) H(1)	H(i)	H(j)	Me-S	Me-N	Coup.const.(Hz) $J_{1,i}$	$J_{1,j}$	$J_{i,j}$
1°	TFA[b]	1	4.62	3.26	3.18	2.21	-	10.6	4.3	-14.6
1°	$CDCl_3$	<<1	4.36	3.11	3.01	2.17	-	10.8	3.9	-14.5
1°	(1:1)[c]	1	4.37	3.02	2.94	2.03	-	7.3	7.0	-14.0
2°	TFA	1	4.25	3.18	3.10	2.10	2.72	10.2	5.0	-14.9
2°	(51:1)[d]	1	4.23	3.18	3.11	2.12	2.66	9.5	5.2	-14.8
2°	(21:1)[d]	1	4.23	3.16	3.08	2.10	2.65	9.5	4.6	-14.7
2°	(9:1)[d]	1	4.23	3.15	3.07	2.11	2.66	9.2	5.3	-14.6
2°	(5:1)[d]	1	4.21	3.15	3.07	2.10	2.64	9.2	5.7	-14.7
2°	(2:1)[d]	1	4.17	3.20	3.06	2.05	2.58	8.2	6.4	-14.2
2°	(1:1)	1	4.11	3.23	3.05	2.04	2.56	7.9	6.8	-14.3
2°	$CDCl_3$	1	4.11	3.45	3.13	2.17	2.73	10.6	4.3	-14.7
2°	(10:1)[c]	2.4	4.16	3.31	3.08	1.97	2.53	6.2	8.4	-13.8
2°	(2:1)[c]	2.4	4.28	3.20	3.04	2.00	2.50	6.6	8.3	-14.0
2°	DMSO-$\underline{d}_6$	4	4.38	3.21	3.07	2.06	2.44	5.7	8.9	-13.8
3°	TFA	1	4.53	3.43	3.22	2.23	2.81/3.02	10.4	5.4	-15.1
3°	(100:1)[d]	1	4.46	3.31	3.18	2.16	-	9.6	6.1	-14.7
3°	(45:1)[d]	1	4.46	3.28	3.16	2.14	-	9.2	6.7	-14.6
3°	(20:1)[d]	1	4.48	3.26	3.16	2.11	-	7.4	7.3	-14.5
3°	(15:1)[d]	1	4.49	3.26	3.16	2.10	-	8.1	7.4	-14.4
3°	(8:1)[d]	1	4.52	3.25	3.16	2.08	-	7.5	8.1	-14.0
3°	(5:1)[d]	1	4.52	3.23	3.17	2.06	-	7.0	8.5	-14.1
3°	(3:1)[d]	1	4.48	3.25	3.19	2.05	-	5.9	9.5	-13.9
3°	(1:1)	1	4.39	3.34	3.27	2.01	-	4.7	10.7	-13.6
3°	$CDCl_3$	1	4.36	3.42	3.34	1.99	2.83	4.2	10.5	-13.4
3°	(8:1)[c]	3	4.45	3.42	3.36	1.99	2.72/2.88	4.4	10.7	-13.6
3°	(2:1)[c]	3	4.57	3.36	3.27	2.02	2.72/2.88	5.5	9.7	-13.6
3°	(1:1)[c]	3	4.60	3.33	3.24	2.02	2.68/2.84	5.1	10.0	-13.7
3°	DMSO-$\underline{d}_6$	3	4.69	3.38	3.34	2.09	-	6.1	8.9	-13.8

[a] % in w/v. [b] All spectra of **1** in TFA:$CDCl_3$ mixtures resulted deceptively simple (200 MHz). [c] $CDCl_3$:DMSO-$\underline{d}_6$ ratio in v/v. [d] TFA:$CDCl_3$ ratio in v/v.

Table 4.- ^{1}H-NMR parameters of sulfonium salt **5** in several solvents (c= 1%).

Solvent		Chem.shifts(ppm) H(1)	H(i)	H(j)	Me-S	Coup.const.(Hz) $J_{1,i}$	$J_{1,j}$	$J_{i,j}$
$CDCl_3$/CD_3CN	(10:1)[a]	5.17	4.45	3.97	2.86/2.94	8.7	6.0	-13.7
"	(1:1)	4.99	4.41	3.84	2.82/2.90	8.8	6.3	-13.6
CD_3CN		4.97	4.36	3.86	2.80/2.88	8.3	6.6	-13.6
$CDCl_3$/DMSO-$\underline{d}_6$	(8:1)[a]	4.98	4.38	4.02	2.93/2.96	8.5	5.2	-13.6
"	(4:1)	5.01	4.42	4.11	3.02/3.06	8.7	5.5	-13.5
"	(2:1)	4.98	4.30	4.08	3.02/3.06	8.5	6.1	-13.4
"	(1:1)	4.96	4.14	4.03	2.98/3.03	8.1	6.5	-13.2
DMSO-$\underline{d}_6$		4.90	3.91[b]		2.94/2.98			
$CDCl_3$	(1.5)[c]	5.38	4.54	4.24	2.66/2.82	6.4	6.9	-13.6
"	(2.0)	5.39	4.57	4.28	2.66/2.82	5.8	7.2	-13.6
"	(3.0)	5.24	4.43	4.19	2.68/2.88	6.0	7.6	-14.0
"	(5.0)	5.27	4.48	4.30	2.72/2.96	5.8	9.2	-13.8
"	(7.0)	5.30	4.49	4.36	2.72/2.97	5.6	9.5	-14.0
TFA		5.33	4.42[b]		2.76/3.06			

[a] v/v ratio; [b] deceptively simple spectra; [c] TFA:substrate molar ratio.

Proton Assignment

The disparity between the two vicinal coupling constants found in $CDCl_3$ in all cases (Table 1) showed that in this solvent a strong preference of either A or B rotamers must exist, where one of the methylenic protons [(H(2) or H(3) in Figure 1] has an anti arrangement and the other a gauche one with respect to H(1). The sense of this preference depends on the assignment of $\delta H(i)$ and $\delta H(j)$ values, deduced from the spectra, to H(2) and H(3). This fact is reflected by the values of the calculated populations collected in Table 5, taking into account the two possible assignments (I: i=2, j=3 and II: i=3, j=2). It should be noted that the preferences observed in $CDCl_3$ and in DMSO-d_6 have been correlated by studying different mixtures of the two solvents (see Table 1); the results are not indicated in Table 5 for the sake of brevity.

Dealing first with steric repulsions, the most stable conformations of compounds **1-3** are depicted in Figure 2, together with their calculated relative energies in KJ/mol[8].

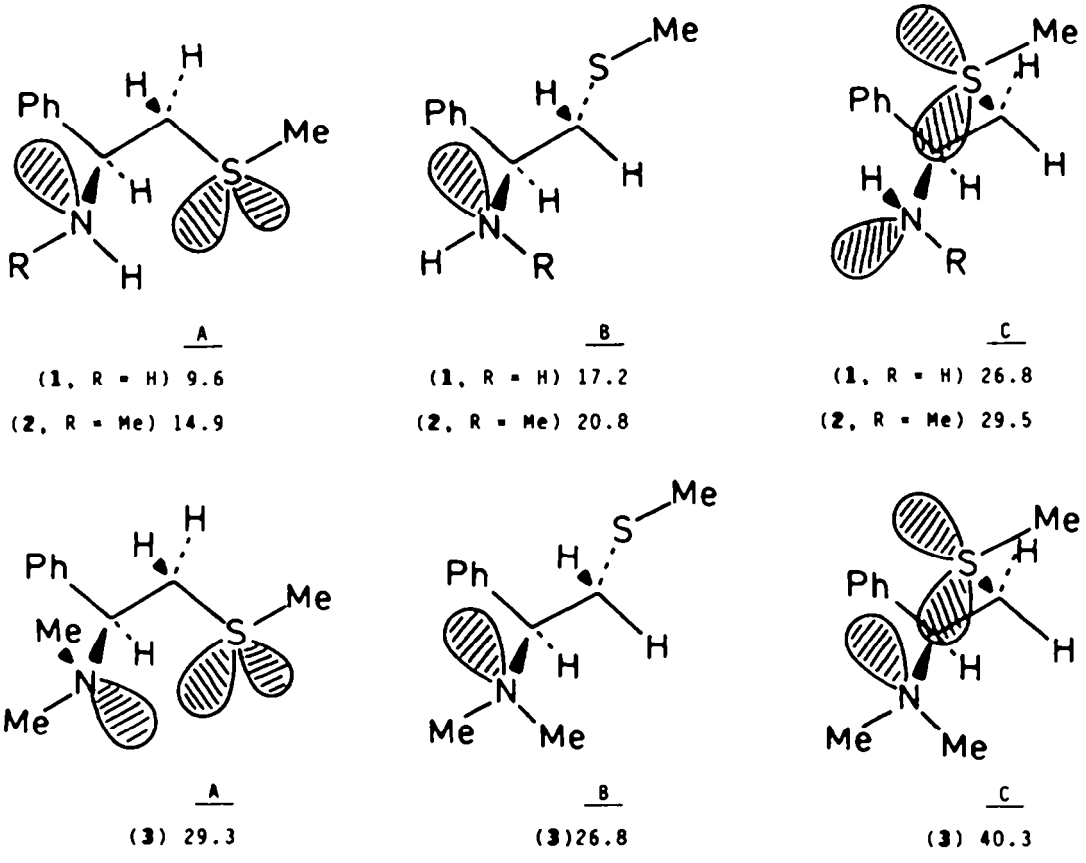


Figure 2.- Most stable conformations of compounds **1** to **3** and their relative energies in KJ/mol (see ref. 8).

Table 5.- Conformational populations (%) of compounds **1** to **4** in $CDCl_3$ and DMSO-$\underline{d}_6$

Comp	Solv	Conc[a]	Assignment I			Assignment II		
			x_A	x_B	x_C	x_A	x_B	x_C
1	$CDCl_3$	10	71	12	17	8	71	21
1	"	1.25	69	14	17	10	69	21
1	DMSO-$\underline{d}_6$	5	57	26	16	23	58	19
2	$CDCl_3$	10	68	19	13	14	68	18
2	"	1.25	72	17	11	12	72	16
2	DMSO-$\underline{d}_6$	5	48	40	13	37	50	13
3	$CDCl_3$	10	25	63	12	62	29	9
3	DMSO-$\underline{d}_6$	4.5	24	67	9	65	29	6
4	$CDCl_3$	>1	-4	102	2	97	22	-19
4	[b]	1	-10	104	6	101	16	-18

[a] % w/v; [b] $CDCl_3$:DMSO-$\underline{d}_6$ (4:1) mixture.

These values, although not usable in a strict quantitative manner, point out firstly that the contribution of C rotamers must be very minor. On the other hand, the relative energies of A and B rotamers indicate that a preference of A must be expected when the amine function is NH_2 or NHMe, whereas the corresponding values for **3** are too close to make any prediction. These facts allow to discard assignment II of Table 5 for **1** and **2** since in that assignment x_B ("and even x_C") is higher than x_A. The uncertainty in the assignment of **3** may be diminished considering the possible repulsive interaction between the electron pairs of heteroatoms that has been observed in similar cases[13]. This destabilizing effect must be undoubtedly present in the A (and C) rotamer of amine **3** to overcome the strong steric $(Me/SMe)_{1,3\text{-}p}$ or $(Me/NMe_2)_{1,3\text{-}p}$ interactions (see Figure 2) that otherwise would take place. Thus, the predominance of rotamer B in this compound (**3**), not very clear from a simple steric viewpoint (see above), can now be fully justified and therefore the asignment II (where $x_A > x_B$) may also be rejected in this case[14]. In amines **1** and **2** this repulsion can easily be avoided by orienting an aminic hydrogen towards sulfur (see Figure 2) and thereby, the formation of intramolecular hydrogen bonding is favored. Unfortunately, our attempts of making the NH...S association[15] evident by ir spectroscopy in these compounds were unsuccessful. Moreover, the populations of compounds **1** and **2** (see Table 5) varied little if at all with concentration, in contrast to what was found for 1-phenyl-2-methylthioethanol[2], suggesting absence of competition between intermolecular

and intramolecular hydrogen bonding and pointing to the unimportance of the latter.

With regard to the ammonium salt **4**, the substitution of the electronic pair on the nitrogen of **3** by a methyl group (see Figure 2) induces severe steric restrictions in the A (and C) rotamer, whereas in B only a $(Me/H)_{1,3-p}$ interaction is added. On the other hand, the positive charge on nitrogen may induce an attraction between the heteroatoms that would compensate the steric repulsion. However, taking into account that each gauche rotamer of thiocholine is only 8.5% populated[16], the assignment I where **4** shows a higher preference of B rotamer must be also chosen[14] for **4**.

With the aim of at least confirming the assignments made for amines **1**, **2** and **3**, we carried out lanthanide shift reagent (LSR) studies. The observed lanthanide induced shifts (LIS) [relative to H(1)] that the different protons underwent when $Eu(fod)_3$ was added to amines **1** and **2** dissolved in $CDCl_3$ are listed in Table 6a (LIS of amine **3** were unfortunately too small to be measured

Table 6a.- Relative LIS of the indicated protons for the amines **1** and **2** in the presence of $Eu(fod)_3$.

Compound	H(1)	H(ortho)	H(i)	H(j)	MeS	MeN
1	1.00	0.28	1.20	0.61	0.35	-
2	1.00	0.34	1.08	0.53	-0.07	0.60

Table 6b.- Calculated optimum Eu position from the LIS of H(1), H(ortho) and H(i) for the amines **1** and **2**.

				Calculated LIS		
Compound	d(A)	θ	ϕ	H(ortho)	H(i)	R
1	1.97	106	172	0.28	1.18	0.010
2	2.00	107	172	0.33	1.07	0.009

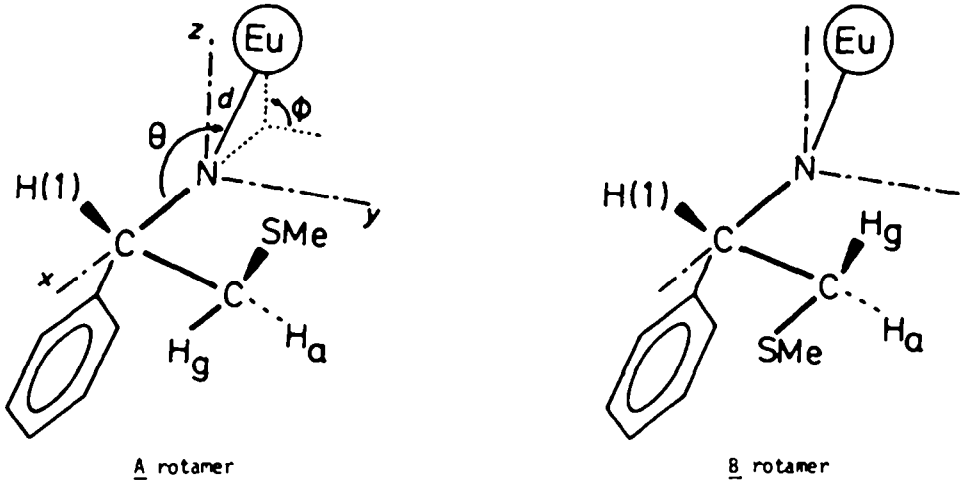
Table 6c.- Calculated relative LIS of H(j) for the amines **1** and **2** in the A or B conformation of Figure 3.

Comp.(rotamer)	Calcd. H(j) LIS	R
1 (A)	0.61	0.001
1 (B)	1.15	0.317
2 (A)	0.57	0.026
2 (B)	1.00	0.303

with reliability). The relatively small LIS observed for MeS suggests that the amine function must be the coordination center as expected.

For a given molecular geometry, there must be a reasonable position of the lanthanide capable of reproducing the observed LIS (see experimental part for calculational details) but, in the case of acyclic structures, the observed LIS for each proton is a weighted mean of its LIS in each conformation[17]. To deal with this problem, we proceeded assuming first that the contribution of rotamer C to the observed LIS is insignificant because its participation in the equilibria must be very small (see above). As concerns rotamers A and B, it may be seen from Figure 3 that the arrangement of H(ortho) (the positions of the two ortho protons have been averaged assuming free rotation of the aromatic ring), H(1) and H(anti) [the proton that exhibits the higher vicinal coupling with H(1)], are the same in both. The optimun lanthanide position can thus be calculated using these three protons. The results are indicated in Table 6b. The arrangement found for europium that best reproduces the observed LIS is almost identical for both compounds and seems to be reasonable, even though the Eu-N distance (d) is at the lower limit of the commonly accepted range (2.0 to 3.5 A[18]). The valence angle Eu-N-C (θ) is close to tetrahedral, and the dihedral angle (ϕ), formed by the Eu-N-C and N-C-C planes, is equivalent to placing the lanthanide in a near anti arrangement with respect to the carbon chain, and at a 68° torsion angle (8° away from the perfect gauche arrangement) with respect to the Ph group.

From the results of Table 6b, the relative LIS of H(gauche) (which displays a very different location in rotamers A and B; see Figure 3) was easily calculated for each conformation. The results for amines **1** and **2** are



A rotamer B rotamer

Figure 3.- Spatial arrangement of protons with respect to the lanthanide shift reagent in A and B conformations.

summarized in Table 6c. It may be seen that a considerable better agreement factor (R) was obtained assuming the geometry of H(gauche) in the A rotamer. These results, in our view, constitute solid support for assignment I of Table 5 for the aminothioethers **1** and **2**, coinciding with the arguments based on steric and polar grounds.

In order to obtain more information about the role of polar interactions, we have studied compounds **1** to **4** in DMSO-$\underline{d}_6$. It may be observed in Table 5 that, whatever the assignment may be, the preference of the predominant rotamer in $CDCl_3$ is attenuated by DMSO-$\underline{d}_6$ for compounds **1** and **2**. As there is little chance of the A rotamers of these two compounds being more stable in DMSO-$\underline{d}_6$ than in $CDCl_3$ (the size of amino group increases[9] and its possible association with sulfur is diminished in that solvent), the assignment II may definitively be rejected for **1** and **2** because it leads to the conclusion that A is more populous in DMSO-$\underline{d}_6$ than in $CDCl_3$ (see Table 5). On the other hand, the dimethylamine **3** is almost unaffected by DMSO-$\underline{d}_6$ (see Table 5) as expected, since the NMe_2 group cannot associate with that solvent. Something similar happens with ammonium salt **4** where populations does not vary substantially with increased solvent polarity. This fact reinforces assignment I where $x_B > x_A$ for this compound (**4**). If the A rotamer were predominat, this would imply an overriding electrostatic attraction in which case a diminution of x_A should be observed when solvent polarity is increased.

Protonation Studies

Once a reasonable basis for conformational analysis and proton assignment had been developed, the shifts of conformational equilibria induced by protonation could be assesed. The calculated populations from the ^{1}H-nmr parameters of amines **1**, **2** and **3** in the presence of TFA (see Table 2) are collected in Table 7 (several intermediate TFA:substrate molar ratios have again been ommited for the sake of brevity).

When the nitrogen is protonated, an electrostatic attraction $^+$N/SMe may be postulated in rotamers A and C and so their relative stabilities should increase. In addition, the $^+$NH group is a better donor of hydrogen than NH in hydrogen bonding and therefore the capability of forming intramolecular associations must increase (provided the counterion is sufficiently solvated so as not to be tightly associated with $^+$NH), this also contributes to delocalizing the positive charge. On the other hand, the increase of volume

Table 7.- Conformational populations (%) of the amines **1** to **3** from $CDCl_3$ to pure TFA.

Comp	Solv	[a]	Conc[b]	Assignment I			Assignment II		
				x_A	x_B	x_C	x_A	x_B	x_C
1	$CDCl_3$	0.0	1.3	71	12	17	8	71	21
1	"	0.8	1.7	53	49	-2	35	64	2
1	"	1.0	1.6	53	46	1	33	62	5
1	"	1.4	1.5	66	39	-4	22	73	5
1	TFA	-	2.1	87	20	-7	0	89	11
2	$CDCl_3$	0.0	2.5	68	19	13	13	69	18
2	"	0.8	2.6	32	61	6	52	45	3
2	"	1.2	2.4	33	65	2	55	48	-2
2	"	2.8	2.8	57	43	0	29	65	0
2	TFA	-	4.8	80	29	-9	8	86	6
3	$CDCl_3$	0.0	10.0	25	63	12	62	29	9
3	"	0.7	3.5	2	89	9	86	23	-9
3	"	1.0	3.3	-2	95	7	92	21	-13
3	"	1.4	2.8	7	90	3	84	29	-13
3	"	3.1	2.3	28	75	-3	64	47	-11
3	TFA	-	6.5	77	38	-15	15	86	-1

[a] TFA:substrate molar ratio. [b] % w/v.

experienced by solvated amine functions when protonated[9] will oppose the preceding stabilizing effects.

It may be observed in Table 7 that the initial conformational preference observed in $CDCl_3$ is increased in TFA for amines **1** and **2**, but inverted for **3**, whatever the assignment may be. If B were the preferred rotamer in TFA (see assignment II in Table 7), steric interactions would be predominant rather than electrostatic ones. This hypothesis collides with the observed decrease of x_B in this assignment when one passes from **1** to **2** in TFA, i.e., when the size of nitrogen function is expected to increase ($^+NH_2Me$ must be larger than $^+NH_3$). Thus, assignment II may once again be discarded. Assignment I must also be correct for thioether **3** because the replacement of the nitrogen lone pair by hydrogen does not introduce substantial steric variations on B rotamer (see Figure 2) but, at the same time, the repulsive gauche effect in rotamer A (and C) is replaced by a possible attractive electrostatic interaction and/or by an intramolecular hydrogen bond. Moreover, the population values of this compound fit very well with those obtained for the other two amines. Thus, the diminution of x_A in TFA from **1** (87%) to **2** (80%) and **3** (77%) (see Table 7) is reasonable because it reflects the increase in size of the ammonium function.

The variation of x_B runs in the opposite direction and is thus also in agreement with the predicted volumes of the nitrogen functions (the negative x_C values will be treated later).

It is interesting to analyze the behavior of compounds **1** to **3** when TFA is present but in limited concentration. The values in Table 7 indicate that the shift of conformational equilibria is not proportional to the amount of TFA added. The participation of the rotamer favored in $CDCl_3$ diminishes after the first additions of TFA, reaching a minimum, and subsequently increases to the maximum value observed in pure TFA. These results can be explained reasonably in terms of assignment I, bearing in mind first that the minimum value of x_A is attained at a TFA:substrate molar ratio close to one and, second, that the solvent at this level of TFA is still $CDCl_3$. The initial change in x_A may thus be the result of an increase in size of the nitrogen function resulting from intermolecular association between the ammonium and trifluoracetate ions (by means of hydrogen bonding and/or the formation of a tight ion pair), in as much as the polarity of the medium is not enough to solvate the ions. This type of ion pairing also inhibits intramolecular electrostatic association with sulfur. Thus, the initial effect of TFA on the equilibria is similar to that exerted by DMSO-$\underline{d}_6$, although to a greater extent (compare Tables 5 and 7). When more TFA is added, the intermolecular association between the ions diminishes since TFA in excess is able to solvate the anion. The intramolecular interactions stabilizing the A rotamers then come into play.

Summing up, protonation studies reinforce in all cases assignment I for amines **1**, **2** and **3**. These results are very significant in the latter compound (**3**) since they confirm the important role played by the repulsive gauche effect between NMe_2 and SMe groups.

To pursue this interesting aspect of protonation, we have studied picrates **1**•, **2**• and **3**• of amines **1**, **2** and **3**, respectively, in order to measure the effects exerted by the counterion and the change of solvent polarity in this case. The conformational populations of the picrates in various solvents, extracted from the ^{1}H-nmr data contained in Table 3, are listed in Table 8. The spectra of **1**• and **3**• in pure DMSO-$\underline{d}_6$ resulted deceptively simple (200 MHz) so that we have included in Table 8 one of the $CDCl_3$:DMSO-$\underline{d}_6$ mixtures used for correlating the parameters in both solvents.

We have also studied the picrates in TFA because in this medium, the behavior of free amines (actually trifluoroacetates) and picrates was expected

Table 8.- Conformational populations (%) of picrates **1°**, **2°** and **3°** in various solvents.

Comp	Solv	Conc[a]	Assignment I			Assignment II		
			x_A	x_B	x_C	x_A	x_B	x_C
1°	$CDCl_3$	<<1	88	21	-9	0	90	10
1°	[b]	1	44	51	5	40	54	5
1°	TFA	1	84	26	-10	4	89	7
2°	$CDCl_3$	1	84	26	-10	4	89	7
2°	DMSO-$\underline{d}_6$	4	23	71	6	64	39	-3
2°	TFA	1	78	33	-12	12	86	2
3°	$CDCl_3$	1	3	88	9	84	24	-8
3°	[b]	1	14	83	3	76	34	-10
3°	TFA	1	79	39	-18	15	89	-4

[a] % w/v; [b] $CDCl_3$:DMSO-$\underline{d}_6$ (1:1) mixture.

to be very similar since the counterions should be quite solvated and their effect thus insignificant. The great similarities found in the ^{1}H-nmr data of "amines" in TFA (Table 2) and their corresponding picrates in TFA (Table 3) support that hypothesis. This fact allowed correlating the assignment I of picrates with the same assignment of amines. The correlation between the parameters in $CDCl_3$ and TFA was carried out by carefully observing the change in equilibrium through numerous $CDCl_3$:TFA mixtures (see Table 3)[19].

The situation for picrates in $CDCl_3$ is similar to that of the corresponding amines in the presence of an equimolecular amount of TFA in $CDCl_3$. The observed population differences (compare Tables 7 and 8) must be attributed to the nature of the counterion. The picrate ion has a large size and the negative charge of phenolic oxygen is delocalized through the aromatic ring so that this anion will have less need for solvation or ion pairing than the trifluoracetate. Accordingly, the intramolecular interactions between the heteroatoms are expected to be less perturbed by ion pairing in the case of picrates. Thus, x_A values of assignment I in $CDCl_3$ for **1°** (88%) and **2°** (84%) are higher than those of **1** (53%) and **2** (32%) in $CDCl_3$ containing one molar equivalent of TFA [see Tables 7 and 8; the participation of A for **3°** and **3** (with one equivalent of TFA) in $CDCl_3$ was negligible in both cases]. In this situation, a polar solvent such as DMSO-$\underline{d}_6$ that can also associate with $^+$N-H groups must reduce the effectiveness of the electrostatic attraction and, at the same time, must considerably increase the size of the ammonium group. The drastic diminuition of x_A in favor of x_B for compounds **1°** and **2°** when the

solvent was changed to DMSO-$\underline{d}_6$ (see Table 8) is in accord with this analysis. In contrast, x_A for **3**[a] increased from 3% in $CDCl_3$ to 14% when an equal part of DMSO-$\underline{d}_6$ was added to the solution (see Table 8). This is an anomaly that cannot be explained unless, for the intermolecular interactions with the solvent to be achieved, the picrate ion must be displaced from the single hydrogen of the $^+NHMe_2$ group, lending to a slight diminution (instead of an increase) of the effective size of the ammonium function.

Finally, we terminate this chapter of protonation studies exploring very briefly the effect of introducing a positive charge on sulfur. The conformational populations for the sulfonium salt **5** (see Scheme 1) in several media, deduced from de ^{1}H-nmr data of Table 4, are collected in Table 9 (we were not able to obtain the sulfonium salts derived for sulfides **2** and **3**). It can be readily observed the striking changes experienced by the equilibrium when TFA is added. The initial preference detected at the lowest levels of TFA (the salt was insoluble in $CDCl_3$ or C_6D_6) is inverted gradually when the TFA:compound ratio is increased. This behavior, similar to that observed in a related compound[4], makes easy in this case the task of proton assignment. The presence of positive charge on both heteroatoms should propitiate a strong electrostatic repulsion between them. Thus, assignment I[14] must be accepted as correct because it implies a preference of B rotamer (the heteroatoms as far from each other as possible; see Figure 1) when TFA is in higher proportion. Therefore, the important consequence is that conformation A is the preferred

Table 9.- Conformational populations (%) of sulfonium salt **5** in several solvent mixtures (c= 1%).

Solvent	Assignment I			Assignment II		
	x_A	x_B	x_C	x_A	x_B	x_C
$CDCl_3/CD_3CN$ (10:1)[a,b]	65	34	2	27	68	5
$CDCl_3$/DMSO-$\underline{d}_6$a(8:1)[a]	65	24	11	19	66	15
" (1:1)[a,c]	57	40	3	34	61	5
$CDCl_3$ (1.5)[d]	36	50	14	42	45	13
$CDCl_3$ (3.0)[d]	28	59	13	51	41	9
$CDCl_3$ (5.0)[d]	18	79	3	68	39	-7
$CDCl_3$ (7.0)[d,e]	16	83	0	72	38	-10

[a] v/v ratio; [b] insoluble in pure $CDCl_3$ or C_6D_6; [c] deceptively simple ^{1}H-nmr spectrum in pure DMSO-$\underline{d}_6$; [d] TFA:substrate molar ratio; [e] deceptively simple ^{1}H-nmr spectra at higher TFA:substrate ratios.

one in the other solvents (see Table 9). The diminution of that preference when the medium polarity was increased is in accordance with a minimization of an electrostatic attraction $N/^{+}S$ (postulated as the stabilizing factor in similar compounds[2,4,20]) and/or an increase of the effective volume of the NH_2 group (see above).

Molecular Distortions

To complete the study of the thioethers, we deal with the problem of angular deformations. It may be observed in Tables 5, 7 and 8 that when the nitrogen bears a positive charge, some populations apparently take on impossible negative values. Of course, these abnormal values should arise from the method itself used to evaluate the populations[5] since Altona's equation[6] is merely an approxiation, though undoubtedly a very good one. However, as in the favored rotamer there must be strong non bonded interactions, the distortions from a perfectly staggered conformation should be another important source of error. In order to explore this hypothesis, we have recalculated the conformational populations using new model couplings (only for the highest populated rotamer) obtained introducing in Altona's equation dihedral angles different from the standard ones.

In the compounds that showed preference for rotamer A when the amine nitrogen was positively charged (all except **3°** and **4** in $CDCl_3$), it was observed that when the heteroatomic functions approached each other by 5^{o} to 10^{o}, x_A remained almost unaltered whereas x_C showed a null. This fact is consistent with the proposed interactions $^{+}N/SMe$ that stabilize these rotamers, since the attractive energy is inversely proportional to the distance between charges. When there are no such interactions (as in non-protonated species) or when they are minimized (as in DMSO-$\underline{d}_6$), the heteroatoms must separate, and this is probably the reason for there being no anomalous negative x_C values in these cases.

On the other hand, it must be noted that the apparently anomalous variation of x_A for **3°** from $CDCl_3$ to DMSO-$\underline{d}_6$ (see above) can be corrected by assuming a small deformation in the preferred rotamer B in $CDCl_3$. If the Ph group moves away 65^{o} from SMe, x_A increases becoming even higher than x_C and simultaneously, very similar to the x_A value observed in DMSO-$\underline{d}_6$.

Finally, with regards to the ammonium salt **4**, the assignment I seemed to be the most probable one but we can analyze, in the light of these calculations, if the negative x_C values of assignment II may be corrected by

assuming a logical deformation in the predominant rotamer. We have observed that x_C reached a null when the heteroatoms approached each other by a change in torsional angle of ca. 15°. This result does not seem reasonable because the strong steric interactions that take place in this case between nitrogen and sulfur groups, must be larger when the functions come nearer and so assignment I is reinforced. On the other hand, the very negative x_A value observed for this salt when DMSO-d_6 was present (see assignment I in Table 5) could be corrected by rotating the Ph and SMe groups only 5° from the perfectly staggered B conformation.

It is important to emphasize that the intention of these last calculations is not quantitative. However, the reasonability found in the calculated trends of groups to separate or approach makes Altona's equation a valuable tool to estimate, at least semiquantitatively, molecular distortions. We have not considered other deformations (for example, of valency angles) that must also introduce variations in the calculations of model coupling constants.

CONCLUSIONS

The main conclusions of this work are as follows:

(1) Compounds **1** and **2** in $CDCl_3$ show a predominance of the rotamer (A) that bears the heteroatoms in gauche arrangement. This preference diminishes in DMSO-d_6 and increases at high concentrations of TFA (salt formation).

(2) Compounds **3** and **4** in $CDCl_3$ exhibit a preference for rotamers B (heteroatoms in anti relationship) which is insensitive to solvent polarity changes and, in the case of **3**, disappears gradually when TFA is added.

(3) Steric factors are fundamental in controlling conformational equilibria of compounds **1**, **2** and **3**, but a possible small contribution of intramolecular hydrogen bonding cannot be dismissed for **1** and **2**. In the dimethylamine **3**, there is an additional factor whose influence is very relevant, viz the repulsive gauche effect between the lone pairs of heteroatoms.

(4) Protonation at nitrogen promotes the appareance of strong attractive alectrostatic interactions, $^{+}$N/SMe, that are able to control the shifts of conformational equilibria to A rotamers in thioethers **1**, **2** and **3**. These interactions are largely minimized by polar solvents (DMSO-d_6) or as a result of the formation of tight ion pairs.

(5) When the ammonium group does not bear any hydrogen atom as in compound **4**, the steric repulsions exceed the possible electrostatic attraction between the heteroatoms.

(6) The sulfonium salt **5** shows a marked preference of the rotamer A in moderated polar media due to the stabilizing N/$^{+}$S interaction[4,20]. That prefence is diminished by polar solvents or eliminated by the presence of TFA.

EXPERIMENTAL PART

General Procedures

Melting points were determined on a Buchi 594392 type S apparatus in open capillary tubes and are uncorrected. Elemental micronalyses were performed by the Instituto de Quimica Organica del CSIC in Madrid with a Perkin-Elmer model 240 analyzer. Ir spectra were recorded under the conditions specified for each compound on a Pye-Unicam SP-1100 spectrometer. Mass spectra were recorded in a Hewlett-Packard 5995 spectrometer at 70 eV. ^{1}H-nmr spectra were recorded in the FT mode on a Varian XL-100-15 spectrometer coupled with a Varian 620/L computer of 16K, transforming 8K data points and in a Bruker WM-200-SY instrument (Aspect 2000 80K computer) transforming 16K data points. Shifts are reported in ppm downfield from internal TMS and are accurate within 0.1 Hz. Analyses of the spectra were carried out by a LAOCON3 program[21] on a Digital VAX 11/780 computer. We estimate the reliability of all values to be within 0.1 Hz, and the root mean square deviations for the calculated and the experimental lines were always better than 0.05 Hz. LSR studies have been performed by adding known amounts of Eu(fod)$_3$ dissolved in $CDCl_3$ to a solution of the compound in the same solvent. Proton isotropic shifts have been plotted against a reference proton (see text) and the relative slopes obtained by linear regression analysis. To perform the calculations for obtaining the optimum position of lanthanide we have writen a simple computer program in Basic, based on the McConell-Roberston equation[22] following the mathematical method described by Armitage et al.[23]. We used observed LIS and standard coordinates for each conformation as input. Then the program moved the lanthanide location over a sphere, calculated the LIS of each proton and compared observed and calculated LIS by means of an agreement factor (R)[19]. Among all the possible lanthanide locations, the program retains that corresponding to the best R value. The program has been run in the computer of the mass spectrometer described above.

2-methylthio-1-phenylethylamine (1).- Method a) 0.05 mol of thionyl chloride in 25 ml of CCl_4 was added to a cooled solution of 0.1 mole of the hydroxythioether (2-methylthio-1-phenylethanol[24] or 2-methylthio-2-phenylethanol[24]). The mixture was stirred 0.5 h at 0°, anhydrous sodium sulfate was then added and the solution filtered. Evaporation of the solvent yielded an oil that was treated with 50 ml of 40% aqueous ammonia (ethanol was added until the solution was clear). The mixture was stirred at room temperature overnight and worked up, yielding a yellowish oil that was destilled under reduced pressure. Method b) Hydrogen chloride was bubbled into a solution of 0.01 mol de hydroxythioether (see above) in $CHCl_3$ at room temperature. The reaction was monitored by ^{1}H-nmr and after ca. 10 min the starting material was no longer observed. The solution was worked up yielding an oil that was treated with ammonia as described above. Yield 73%; b.p. 59-60°(0.1 mm Hg); mass spectrum m/e (relative intensity) 107(8.7), 106(100), 79(33), 77(15), 91(3); ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 2H), 2.07 (s, 3H), 2.73 (m, 2H), 4.10 (m, 1H), 7.36 (m, 5H); IR (neat) 3380 (NH_2), 3075, 3040, 2920, 1600, 1585, 1490, 1450, 760, 730, 695 cm^{-1}. Picrate (**1**'):- M.p. 175-176°; ^{1}H NMR (acetone-d_6) δ 2.10 (s, 3H), 3.32 (m, 2H), 4.78 (m, 1H), 7.40-7.68 (m, 5H), 8.74 (s, 2H). Anal. ($C_{15}H_{16}O_7N_4S$) C, H, N, S.

N-methyl-2-methylthio-1-phenylethylamine (2).- It was obtained by the same methods as **1** using 40% methylamine instead of ammonia. Yield 69%; b.p. 78-80° (1 mm Hg); mass spectrum m/e (relative intensity) 121(9), 120(100), 91(5), 42(49).; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 1H), 2.07 (s, 3H), 2.30 (s, 3H), 2.74 (m, 2H), 3.63 (m, 1H), 7.32 (m, 5H); IR (neat) 3330 (NH), 3075, 3035, 2920, 1490, 1475, 1450, 1440, 1140, 730, 700 cm^{-1}. Picrate (**2**'):- M.p. 158-159°; ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.73 (s, 3H), 3.29 (m, 2H), 4.08 (m, 1H), 7.52 (m, 5H), 8.96 (s, 2H). Anal. ($C_{16}H_{18}O_7N_4S$) C, H, N, S.

N,N-dimethyl-2-methylthio-1-phenylethylamine (3).- Obtained by the same methods as **1** using 40% dimethylamine instead of ammonia. Yield 81%; b.p. 92-94° (0.6 mm Hg); mass spectrum m/e (relative intensity) 135(12), 134(100), 118(4), 91(9), 77(8); ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.25 (s, 6H), 3.01 (m, 2H), 3.52 (m, 1H), 7.32 (m, 5H); IR (neat) 3050, 2940, 2885, 2840, 2800, 1500,

1460, 740, 700 cm^{-1}. **Picrate (3')**.- M.p. 126-128°; ^1H NMR ($CDCL_3$) δ 1.99 (s, 3H), 2.83 (s broad, 6H), 3.58 (m, 2H), 4.36 (m, 1H), 7.50 (m, 5H), 8.92 (s, 2H). Anal. ($C_{17}H_{20}O_7N_4S$) C, H, N, S.

2-methylthio-1-phenylethyl trimethyl ammonium iodide (4).- A mixture of 1 mmol of **3** and 10 mmol of methyl iodide in 5 ml of $CHCl_3$ was stirred for 1 h. and the precipitate filtered and recrystallized from CH_2Cl_2. Yield 94%; m.p. 175-177° (dec.); ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H), 3.42 (m, 2H), 3.46 (s, 9H), 5.39 (m, 1H), 7.57 (m, 5H); IR (KBr) 3020, 2940, 1465, 1440, 1420, 970, 955, 860, 800, 755, 725, 705 cm^{-1}. Anal. ($C_{12}H_{20}NSI$) C, H, N.

2-amino-2-phenylethyl dimethyl sulfonium p-toluensulfonate (5).- A mixture of 10 mmol of thioether **1** and 30 mmol of methyl p-toluensulfonate is stirred at 30° for 48 h. The resulting oil is washed several times with anhidrous ethyl ether and the solid filtered and recrystalized from ethyl acetate-ethanol (3:1). M.p. 176-180°; ^1H NMR (CD_3CN) δ 2.21 (s broad, 2H), 2.33 (s, 3H), 2.78 (s, 3H), 2.86 (s, 3H), 3.86-4.36 (m, 2H), 4.97 (m, 1H), 7.40 (m, 9H); IR (KBr) 3370, 1595, 1185, 1010, 735 and 700 cm^{-1}.

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REFERENCES AND NOTES

(1) Part 14, E. Brunet, J.L. García Ruano, J.H. Rodríguez and F. Alcudia, Tetrahedron, **1984**, 40, 4433.

(2) F. Alcudia, F. Fariña, J.L. García Ruano and F. Sánchez, J. Chem. Soc., Perkin Trans. II, **1978**, 412.

(3) "Burger's Medicinal Chemistry" (ed. M.E. Wolff), Wiley New York 1981, 4th edn., Part III, p. 487.

(4) E. Brunet, M.C. Carreño, M.T. Gallego, J.L. García Ruano and F. Alcudia, J. Chem. Soc., Perkin Trans. II, **1983**, 937.

(5) E. Brunet, J.L. García Ruano, M.A. Hoyos, J.H. Rodríguez, P.Prados and F. Alcudia, Org. Magn. Reson., **1983**, 21, 643.

(6) C.A.G. Hassnot, F.A.A.M. de Leeuw and C. Altona, Tetrahedron, **1980**, 36, 3403.

(7) We used an electronegativity value for ^+N increased in 0.5 units with respect to that of the neutral N.

(8) It was not possible to make molecular mechanics calculations since the torsional parameters for the fragment N-C-C-S were not available. The calculated values were simply obtained considering, on the one hand, the gauche interactions around the C-C bond [(N/SMe) and (Ph/SMe) evaluated from the A values of the NR_2[9], Ph[10] and SMe[11] groups] and, on the other hand, those around the C-N bond [(Ph/Me) evaluated as 6.2 KJ/mol[12]]. The 1,3-parallel (1,3-p) interactions have been also taken into account [(Me/H) estimated as 3.6 KJ/mol on carbon skeletons[12]]

(9) E.L. Eliel, E.W. Della and T.H. Williams, Tetrahedron lett., **1963**, 831; H. Feltkamp, N.C. Franklin, K.D. Thomas and W. Brugel, Ann., **1965**, 683, 64; J. Sicher, J. Jonas and M. Tichy, Tetrahedron lett., **1963**, 825.

(10) E.W. Garbisch jr. and D.B. Patterson, J. Am. Chem. Soc., **1963**, 85, 3228.

(11) F.R. Jensen, C.H. Bushweller and B.H. Beck, J. Am. Chem. Soc., **1969**, 91, 344.

(12) C.A. Ibarra, M.S. Arias, F. Fernández y M. Rico, Org. Magn. Reson., **1977**, 19, 251.

(13) N.S. Zefirov, G.L. gurvich, A.S. Shaskov, M.Z. Krimer and E.A. Vorob'eva, Tetrahedron, **1976**, 32, 1211.

(14) The numbering of the assignments (I or II) is arbitrary; it was chosen et post facto to make I the preferred assignment in all cases.
(15) J.D. Schribner and J.A. Miller, J. Org. Chem., **1967**, 32, 2348; B.D. Andrewas, J.D. Raeh and D.E. Reichert, Tetrahedron lett., **1969**, 1859; P.J. Krueger, Tetrahedron, **1970**, 26, 4753.
(16) N.J.M. Birdsall, P. Partington, N. Datta, P. Mondal and P.J. Pauling, J. Chem. Soc., Perkin Trans. II, **1980**, 1415; P. Partington, J. Feeney and S.V. Burgen, Mol. Pharmacol., **1972**, 8, 269.
(17) In these cases the situation can be obscured by the fact that LSR may affect the composition of equilibria[18]. We did not observe variations of the vicinal couplings along the experiment but this argument cannot be used as evidence of absence of side effects. Substantial increments in chemical shifts can be observed even when the mole fraction of complexed substrate is quite small. Thus, conformational ratios can be quite different in the complex and yet show little effect on coupling constants. Nevertheless, the validity of the experiment lays on the very reasonable results obtained.
(18) O. Hofer, Top. Stereochem. **1976**, 9, 111.
(19) Unfortunatelly all spectra of **1**° at intermediate TFA:$CDCl_3$ mixtures resulted deceptively simple even at 200 MHz. Thus, the correlation of the proton assignment between these solvents was based on the correlation of **2**°.
(20) F. Alcudia and E.L. Eliel, J. Am. Chem. Soc., **1974**, 96, 1939.
(21) S.M. Castellano, "LAOCN3 in Computer Programs for Chelistry", ed. D.F. Detar, Benjamin, New York, 1968 vol 1, p 10.
(22) H.M. McConnell and R.E. Roberston, J. Chem. Phys., **1958**, 29, 1361.
(23) I.M. Armitage, L.D. Hall, A.G. Marshall and L.G. Werbelow, J. Am. Chem. Soc., **1973**, 95, 1437.
(24) F. Alcudia, E. Brunet, J.L. García Ruano, J. Rodríguez and F. Sánchez, J. Chem. Research, (M) **1982**, 2810; (S) **1982**, 284.