Tetrahedron Vol. 42, No. 5, pp. 1423 to 1438, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00

STEREOCHEMISTRY OF ORGANIC SULFUR COMPOUNDS. PART 20[#]. CONFORMATIONAL ANALYSIS OF AMINOSULFOXIDES AND SULFONES

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(*Received in UK 30 September* 1985)

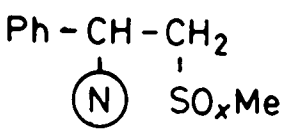
Summary: Synthesis and conformational analysis of 1-phenyl-2-methylsulfinyl- (and -sulfonyl-) ethylamine (and its N-methyl and N,N-dimethylderivatives) are reported. Conformational preferences have been determined by carefully observing the changes of the vicinal coupling constants with protonation in the ^{1}H-nmr spectra. The strongly configuration dependent conformational behavior displayed by sulfoxides is explained in terms of a previously proposed donor-acceptor interaction between nitrogen and sulfur. Conformational equilibria of sulfones are controlled by steric interactions except when nitrogen is protonated in which case a relatively weak electrostatic attraction takes place between the heteroatomic functions.

INTRODUCTION

Recent work has suggested that the different conformational behavior displayed by the diastereomers of β-oxygenated sulfoxides may be explained in terms of a n -> d donor-acceptor interaction, strongly configuration dependent, between a lone pair of the oxygen in β and an adequately oriented d orbital at sulfur[1]. On the other hand, earlier studies on β-aminosulfoxides showed similar differences in the bahavior of the corresponding diastereomers[2], suggesting that this n -> d donor-acceptor interaction may be also operative between amine and sulfoxide groups. Since the donor ability of nitrogen lone pair in its interaction with sulfinyl group may be easily modified by reaction with an acid, a systematic study of the conformational changes to be observed when β-aminosulfoxides are protonated is very desirable concerning the investigation of the proposed n -> d donor-acceptor interaction[1]. In addition, we have shown in previous work that the detailed study of these protonation induced conformational changes in a series of β-aminothioethers[3] suggested that careful observation of the non-monotonic population variations -provoked by the gradual addition of trifluoracetic acid to the aminothioether dissolved in chloroform- is a powerful tool for determining the conformational preferences of these systems. We thus report in the present work the synthesis and conformational

[#] Part 19. E. Brunet, M.C. Carreño, J.M. Rodríguez and J.L. García Ruano, An. Quím., in the press.

analysis by the aforementioned protonation method[3] of the β-aminosulfoxides indicated in Scheme 1, as well as the corresponding sulfones, as the first systematic study of the nature of the interactions between amine and sulfoxide or sulfone functions. The relative configuration of the diastereomeric sulfoxides and the qualitative importance of the n -> d donor acceptor interaction[1] were determined as part of the investigation.



Compound	N	x
1	NH_2	1
2	NHMe	1
3	NMe_2	1
4	NH_2	2
5	NHMe	2
6	NMe_2	2

Scheme 1

RESULTS

Synthesis

Sulfoxides 1 and 2 and sulfones 4 and 5 were prepared by oxidization of the corresponding thioethers[3] with 1 eq. or excess, respectively, of sodium metaperiodate or m-chloroperoxybezoic acid. The two diastereomers obtained in the preparation of the sulfoxides (in a 1:1 ratio as measured by integration of the corresponding CH_3-SO signals in the ^{1}H-nmr spectrum) were separated by fractional crystallization in the case of 1. The higher melting isomer (mp. 115-117°C) was arbitrarily designated α and its epimer (mp. 70-72°C) β. In the case of 2 it was necessary to convert the diastereomeric mixture into the picrate salts for partial separation by fractional crystallization. Treatment of the epimeric picrates with base afforded analytical samples of the two diastereomers of 2 in a purity adequate for performing appropiate nmr measurements. The oxidization method failed in the case of the dimethylamino-sulfoxides 3 and -sulfone 6. Their synthesis was therefore accomplished by addition of aqueous dimethylamine to β-methylsulfinyl- or β-methylsulfonylstyrene, respectively. The sulfoxides 3 could not be separated in our hands but were independently prepared by methylation of each diastereomer of 1 with formaldehyde in formic acid[4]. A modified methylation procedure, using formaldehyde and sodium borohydride[5], gave a mixture of the starting material 1 (α or β), the N-methyl- 2 and N,N-dimethylsulfoxides 3 (α or β) in ca. 1:1:1 ratio as determined by ^{1}H-nmr. This reaction, though not useful from a synthetic point of view, served to correlate

the α (and β) isomers of sulfoxides 1, 2 and 3. Thus, diastereomeric sulfoxides of the same designation (α or β) have the same relative configuration of their two (benzyl carbon and sulfur) chiral centers.

Conformational analysis

General Considerations

The analysis of the ^{1}H-nmr spectra of compounds 1-6, recorded under several conditions, led to the chemical shifts and coupling constants listed in Table 1. The observed vicinal coupling constants are a weighted average of those of the individual rotamers in equilibrium (Fig. 1). The disparity found in all the cases between the two vicinal couplings $J_{1,2}$ and $J_{1,3}$ in $CDCl_3$ (see Table 1) indicates a marked predominance of either conformer A or conformer B (see Fig. 1) in this solvent. Which one of them is preferred depends on the assignment of protons H(2) and H(3) of Fig. 1 to the spectral signals H(i) and H(j) of Table 1. We have calculated the populations contained in Tables 2 to 4 in the usual manner[6] taking into account both proton assignments ("solutions 1 and 2") and arbitrarily arranging the assignments in such a way that solution 1 corresponds in all the cases to a preference, in $CDCl_3$, of rotamer A.

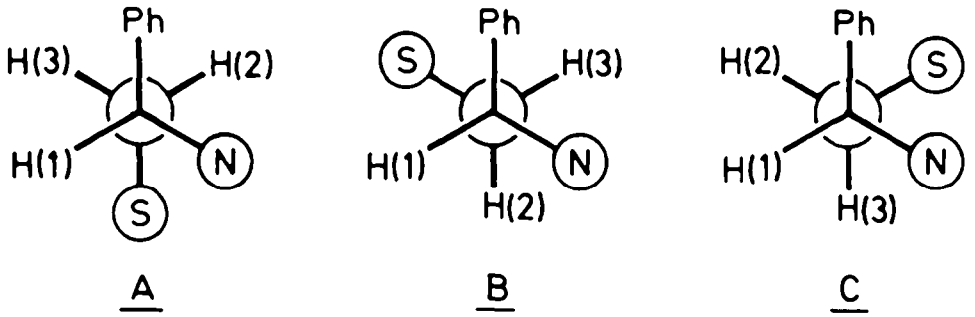


Figure 1.- Staggered rotamers around the C(1)-C(2) bond.

The conformational preference in other solvents has been correlated to that in $CDCl_3$ by carefully observing the evolution of equilibria in numerous solvent mixtures (see Table 1), several of them being omitted in Tables 2-4 for the sake of brevity.

The generally small value of $\Delta\delta$ between the methylenic protons precludes any chemical shift criterion from being used to solve the uncertainty as to which conformer, A or B, is preferred in $CDCl_3$. This task is accomplished (see below) by a careful study of the conformational changes induced by the gradual addition of trifluoracetic acid (TFA) to each aminosulfoxide or sulfone dissolved in

Table 1.- ^{1}H-nmr parameters for compounds 1 to 6 in various solvents.

Comp	Solv(c[a])	TFA:substrate molar ratio	Chemical Shifts (ppm) H(i)	H(i)	H(j)	Me-S	Me-N	Coup. consts. (Hz) $J_{1,i}$	$J_{1,j}$	$-J_{i,j}$
1α	$CDCl_3$(5)	--	4.59	2.92	2.97	2.62	--	10.5	3.3	12.9
	" (1.3)	--	4.60	2.92	2.97	2.61	--	10.4	3.3	12.8
	" (3)	0.17	4.60	2.96[b]		2.62	--	14.0[c]		-
	" (3)	0.47	4.64	3.11	2.98	2.60	--	10.2	2.8	13.3
	" (3)	0.80	4.71	3.50	3.05	2.66	--	10.0	3.3	13.5
	" (3)	1.00	4.89	3.68	2.97	2.60	--	9.3	2.4	13.8
	" (3)	3.00	5.04	3.77	3.20	2.73	--	9.5	2.5	14.3
	" (3)	5.15	5.10	3.84	3.33	2.85	--	9.8	2.4	14.5
	" (3)	>25.00	--	3.94	3.51	2.96	--	9.7	3.1	14.7
	TFA(3)	--	5.38	4.07	3.72	3.04	--	9.5	3.6	14.8
	8:1[d](1.5)	--	4.55	2.98[b]		2.64	--	13.7[c]		-
	2:1[d] 1.5)	--	4.44	3.03	2.91	2.63	--	10.8	2.8	12.8
	1:1[d](1.5)	--	4.36	3.03	2.87	2.60	--	10.8	3.2	12.9
	DMSO-$\underline{d}_6$(2)	--	4.21	2.99	2.81	2.57	--	10.8	3.3	12.8
2α	$CDCl_3$(1)	--	4.13	2.93[b]		2.59	2.32	13.5[c]		-
	" (0.5)	0.25	4.32	3.23	3.06	2.62	2.38	9.8	3.4	13.4
	" (0.5)	0.49	4.52	3.54	3.19	2.64	2.45	8.8	3.8	13.8
	" (0.5)	0.96	4.75	3.87	3.33	2.69	2.53	7.9	3.9	14.1
	" (0.5)	1.92	4.82	3.89	3.35	2.77	2.58	8.7	3.3	14.3
	" (0.5)	3.84	4.84	3.89	3.40	2.81	2.62	8.8	2.7	14.3
	4:1[d](0.5)	--	4.06	3.03	2.89	2.59	2.27	10.6	3.2	13.1
	2:1[d](0.5)	--	4.01	3.07	2.85	2.59	2.23	10.6	3.4	13.1
	1:1[d](0.5)	--	3.97	3.08	2.82	2.57	2.20	10.7	3.5	13.1
3α	$CDCl_3$(1.4)	--	4.11	3.35	2.99	2.61	2.20	10.8	4.4	13.1
	" (1.3)	0.25	4.23	3.56	3.06	2.60	2.33	9.7	4.9	13.3
	" (1.2)	0.50	4.34	3.77	3.12	2.59	2.46	8.6	5.0	13.6
	" (1.2)	0.75	4.47	3.99	3.20	2.57	2.60	7.3	5.5	13.8
	" (1.2)	1.00	4.59	4.21	3.27	2.55	2.75	6.2	5.9	14.2
	" (1.1)	1.50	4.70	4.26	3.34	2.58	2.80	5.9	5.9	14.1
	" (1.0)	2.00	4.77	4.26	3.39	2.62	2.82	6.1	5.9	14.1
	" (1.0)	3.00	4.88	4.28	3.48	2.70	2.85	6.5	5.6	14.4
	TFA(1)	--	5.15	4.14	3.90	2.98	3.1/2.9	6.7	5.9	15.0
	DMSO-$\underline{d}_6$(10)	--	4.09	3.66	2.84	2.56	2.19	11.2	4.9	13.3

[a] %w/v. [b] Deceptively simple spectrum. [c] $J_{1,i}+J_{1,j}$ value. [d] $CDCl_3$:DMSO-$\underline{d}_6$ mixture.

Table 1 (cont.)

Comp	Solv(c[a])	TFA:substrate molar ratio	Chemical Shifts (ppm) H(1)	H(i)	H(j)	Me-S	Me-N	Coup. consts. (Hz) $J_{1,i}$	$J_{1,j}$	$-J_{i,j}$
1β	$CDCl_3$(10)	--	4.51	3.12	2.87	2.58	--	8.0	5.9	13.0
	" (1.3)	--	4.56	3.11	2.88	2.60	--	8.0	5.6	12.8
	(1)	0.58	4.66	3.45	2.98	2.54	--	7.7	6.2	13.0
	(1)	1.48	4.81	3.67	3.08	2.49	--	8.0	5.8	13.4
	(1)	3.09	4.90	3.80	3.20	2.68	--	9.1	5.0	13.6
	(1)	5.03	--	3.92	3.28	2.82	--	9.3	4.4	13.8
	(1)	>25.00	--	4.01	3.41	2.94	--	9.2	4.6	14.0
	TFA(1)	--	5.29	4.13	3.68	3.04	--	8.6	5.8	13.7
	8:1[d](1)	--	4.52	3.11	2.92	--	--	8.1	5.7	12.8
	4:1[d](1)	--	4.48	3.10	2.95	--	--	7.9	6.0	12.9
	2:1[d](1)	--	4.43	3.08	2.96	--	--	7.9	6.0	12.8
	DMSO-$\underline{d}_6$(1)	--	4.25	3.01	2.95	2.55	--	7.6	6.5	13.0
2β	$CDCl_3$(5)	--	4.07	3.16	2.81	2.56	2.29	7.6	6.4	13.0
	" (0.6)	--	4.07	3.15	2.80	2.56	2.30	7.7	6.2	12.9
	" (1)	0.19	4.16	3.38	2.89	2.61	2.34	7.7	6.1	13.0
	" (1)	0.44	4.30	3.65	3.03	2.65	2.41	7.7	6.5	13.1
	" (1)	0.76	4.46	3.91	3.18	2.80	2.48	7.4	7.2	13.1
	" (1)	1.27	4.56	4.00	3.26	2.73	2.53	7.2	7.1	13.6
	" (1)	2.54	4.62	4.09	3.27	2.82	2.58	8.1	5.8	13.6
	" (4.8)	4.00	4.80	4.04	3.41	2.88	2.70	7.8	6.2	13.7
	" (4.8)	>20.00	4.82	4.04	3.43	2.90	2.70	8.0	6.3	13.7
	TFA(4.5)	--	4.94	4.07	3.63	3.00	2.86	7.7	6.9	13.8
	DMSO-$\underline{d}_6$(3.8)	--	3.95	3.16	3.00	2.63	2.18	7.3	7.1	13.8
3β	$CDCl_3$(1.3)	--	3.82	2.99	3.46	2.54	2.22	9.5	6.2	12.8
	" (1.3)	0.23	3.95	3.15	3.49	2.57	2.36	10.1	5.6	12.7
	" (1.2)	0.51	4.12	3.38	3.54	2.60	2.54	10.9	4.8	12.6
	" (1.2)	1.01	4.39	3.69	3.62	2.65	2.80	11.8	3.1	12.4
	" (1.1)	1.59	4.46	3.71[b]		2.69	2.83	15.6[c]		-
	" (1.0)	3.00	4.59	3.80	3.85	2.72	2.84	10.7	4.7	12.9
	TFA(1)	--	5.07	3.86	4.20	3.22	3.3/3.1	9.5	6.2	13.5
	4:1[d](10)	--	3.98	3.17	3.45	2.57	2.21	9.8	5.8	12.8
	2:1[d](10)	--	4.00	3.22	3.43	2.60	2.19	10.0	5.8	12.8
	1:1[d](10)	--	4.00	3.24	3.41	2.60	2.18	10.2	5.9	12.9
	DMSO-$\underline{d}_6$(10)	--	3.99	3.34[b]		2.59	2.10	-	-	-

[a] %w/v. [b] Deceptively simple spectrum. [c] $J_{1,i}+J_{1,j}$ value. [d] $CDCl_3$:DMSO-$\underline{d}_6$ mixture.

Table 1 (cont.)

Comp	Solv(c[a])	TFA:substrate molar ratio	Chemical Shifts (ppm) H(1)	H(i)	H(j)	Me-S	Me-N	Coup. consts. (Hz) $J_{1,i}$	$J_{1,j}$	$-J_{i,j}$
4	$CDCl_3$(10)[e]	--	4.63	3.35	3.24	2.92	--	9.8	3.0	14.2
	" (1.3)[e]	--	4.66	3.35	3.25	2.94	--	9.8	3.1	14.3
	" (1)	0.20	4.70	3.53	3.29	2.92	--	9.8	3.0	14.2
	" (1)	0.45	4.75	3.71	3.34	2.90	--	9.1	3.4	14.5
	" (1)	1.00	4.92	4.21	3.48	2.85	--	9.1	4.0	14.6
	" (1)	2.16	5.00	4.19	3.51	2.95	--	10.0	3.0	14.6
	" (2)	4.00	5.12	4.24	3.61	2.98	--	10.8	2.6	14.7
	" (2)	>20.00	5.16	4.28	3.67	3.04	--	10.7	2.7	14.9
	TFA(2.5)	--	5.34	4.37	4.01	3.20	--	9.9	3.7	15.0
	DMSO-$\underline{d}_6$(10)[e]	--	4.35	3.45	3.27	2.99	--	9.5	3.6	14.3
5	$CDCl_3$(10)[f]	--	4.16	3.39	3.21	2.86	2.27	9.2	3.8	14.5
	" (1.3)	--	4.18	3.38	3.21	2.86	2.28	9.4	3.7	14.3
	" (1.3)	0.16	4.24	3.56	3.29	2.85	2.32	8.9	4.2	14.4
	" (1.3)	0.36	4.33	3.75	3.41	2.81	2.36	8.2	5.0	14.5
	" (1.3)	0.64	4.45	4.00	3.58	2.73	2.41	7.0	6.3	14.7
	" (1.3)	1.04	4.76	4.34	3.83	2.66	2.51	6.1	7.6	14.6
	" (1.3)	2.08	4.74	4.43	3.67	2.90	2.60	8.2	4.8	14.9
	" (2.7)	4.00	4.84	4.37	3.68	3.03	2.58	9.5	3.8	14.6
	" (2.7)	>15.00	4.88	4.36	3.73	3.08	2.74	9.4	3.7	14.8
	TFA(1.3)	--	5.04	4.40	3.96	3.15	2.85	8.9	4.4	14.8
	DMSO-$\underline{d}_6$(5)[g]	--	4.07	3.63	3.32	3.03	2.17	9.1	4.1	14.5
6	$CDCl_3$(5)[h]	--	4.20	3.75	3.23	2.84	2.17	8.9	5.3	14.9
	" (3)	0.12	4.21	3.76	3.27	2.83	2.10	8.5	5.3	14.9
	" (4.4)	0.25	4.35	3.93	3.57	2.76	2.38	6.8	6.9	14.6
	" (2.8)	0.50	4.46	4.08	3.88	2.66	2.60	4.2	9.1	14.9
	" (2.8)	0.75	4.64	4.23	4.16	2.58	2.76	2.8	10.3	14.6
	" (4.4)	1.00	4.73	4.16[b]		2.58	2.78	-	-	-
	" (2.8)	1.50	4.80	4.15	4.11	2.64	2.84	2.7	10.5	14.9
	" (2.8)	2.00	4.82	4.17	4.06	2.70	2.8/2.9	4.1	9.1	14.6
	" (2.5)	3.00	4.87	4.22	4.05	2.76	2.8/3.0	4.8	8.4	14.5
	" (2.5)	5.00	4.92	4.25	4.04	2.83	2.8/3.0	5.3	8.1	14.7
	" (2.5)	>15.00	4.96	4.28	4.04	2.90	2.8/3.0	5.7	7.5	14.7
	TFA_d(3.2)[h]	--	5.17	4.39	4.10	3.08	2.9/3.1	7.7	6.0	15.1
	5:1[d] (5)[h]	--	4.20	3.79	3.21	2.88	2.17	9.1	5.0	14.9
	2:1[d] (5)[h]	--	4.18	3.87	3.20	2.91	2.16	9.2	5.0	14.9
	1:1[d] (5)[h]	--	4.22	4.02	3.26	2.98	2.14	9.3	5.0	14.9
	DMSO-$\underline{d}_6$(5)	--	4.30[b]		3.35	3.05	2.18	-	-	-

[a] %w/v. [b] Deceptively simple spectrum. [c] $J_{1,i}+J_{1,j}$ value. [d] $CDCl_3$:DMSO-$\underline{d}_6$ mixture.

Long range couplings observed: [e] $J_{i,\underline{Me}S}$= $J_{j,\underline{Me}S}$= 0.65 Hz. [f] $J_{i,\underline{Me}S}$= $J_{j,\underline{Me}S}$= 0.62 Hz. [g] $J_{i,\underline{Me}S}$= 0.62 Hz; $J_{j,\underline{Me}S}$= 0.72 Hz. [h] $J_{i,\underline{Me}S}$= 0.50 Hz; $J_{j,\underline{Me}S}$= 0.95 Hz.

Table 2.- Rotamer populations for α sulfoxides 1, 2 and 3 in various solvents.

Compound	Solvent	TFA:substrate molar ratio	Solution 1 (%) x_A	x_B	x_C	Solution 2 (%) x_A	x_B	x_C
1α	$CDCl_3$	--	86	3	11	-3	85	18
	"	0.5:1	86	5	9	-10	82	28
	"	1.0:1	79	-1	22	-11	70	41
	"	3.0:1	80	0	20	-11	72	39
	TFA	--	77(76)	14(7)	9(17)	0(2)	76(75)	24(23)
	DMSO-$\underline{d}_6$	--	90	4	6	-3	90	13
2α	$CDCl_3$[a]	--	87	3	10	-4	86	18
	$CDCl_3$	0.5:1	70	14	16	3	67	30
	"	1.0:1	60	14	26	8	55	37
	"	3.8:1	72(68)	1(-3)	27(35)	-6(-7)	63(65)	43(42)
	DMSO-$\underline{d}_6$[b]	--	89	6	5	-1	89	12
3α	$CDCl_3$	--	88	17	-5	9	89	2
	"	0.5:1	63	30	7	16	67	17
	"	1.0:1	37	35	28	32	38	30
	"	3.0:1	40	32	28	29	41	30
	TFA	--	42(43)	36(32)	22(26)	30(31)	45(43)	25(27)
	DMSO-$\underline{d}_6$	--	91	23	-15	14	94	-8

[a] $CDCl_3$:DMSO-$\underline{d}_6$(4:1) mixture; deceptively simple spectra at higher $CDCl_3$ concentration. [b] $CDCl_3$:DMSO-$\underline{d}_6$ (1:1) mixture; deceptively simple spectra at higher DMSO-$\underline{d}_6$ concentration.

Table 3.- Rotamer populations for β sulfoxides 1, 2 and 3 in various solvents.

Compound	Solvent	TFA:substrate molar ratio	Solution 1 (%) x_A	x_B	x_C	Solution 2 (%) x_A	x_B	x_C
$^1\beta$	$CDCl_3$	--	56	30	14	26	58	16
	"	0.6:1	51	42	7	31	58	11
	"	1.5:1	55	38	7	26	61	13
	"	5.0:1	72	23	5	8	73	18
	TFA	--	61(62)	39(32)	0(6)	24(27)	68(64)	8(9)
	DMSO-$\underline{d}_6$	--	50	41	9	37	52	11
$^2\beta$	$CDCl_3$	--	51	37	12	33	54	13
	$CDCl_3$	0.8:1	44	53	2	41	56	3
	"	1.3:1	43	53	4	42	54	5
	"	4.0:1	52	42	6	30	59	11
	TFA	--	48(50)	51(45)	1(5)	38(41)	59(54)	3(5)
	DMSO-$\underline{d}_6$	--	45	48	7	44	49	7
$^3\beta$	$CDCl_3$	--	71	38	-9	30	75	-5
	"	0.5:1	86	32	-18	7	94	-1
	"	1.0:1	101	12	-13	-13	102	11
	"	3.0:1	85	30	-15	6	92	2
	TFA	--	69(72)	46(37)	-14(-9)	24(30)	81(75)	-5(-5)
	DMSO-$\underline{d}_6$ [a]	--	80	34	-14	26	83	-9

[a] $CDCl_3$:DMSO-$\underline{d}_6$ (1:1) mixture; deceptively simple spectra at higher DMSO-$\underline{d}_6$ concentration.

Table 4.- Rotamer populations for sulfones 4, 5 and 6 in various solvents.

Compound	Solvent	TFA:substrate molar ratio	Solution 1 (%) x_A	x_B	x_C	Solution 2 (%) x_A	x_B	x_C
4	$CDCl_3$	--	83	-2	19	-6	81	25
	"	0.5:1	76	10	14	-3	73	30
	"	1.0:1	74	16	10	3	73	24
	"	4.0:1	96	3	1	-17	93	24
	TFA	--	83(82)	15(7)	2(11)	-3(1)	83(82)	20(17)
	DMSO-$\underline{d}_6$	--	79	4	17	0	77	23
5	$CDCl_3$	--	77	5	19	1	75	23
	$CDCl_3$	0.6:1	44	43	13	34	50	16
	"	1.0:1	28	62	10	49	44	7
	"	4.0:1	78	15	7	0	70	30
	TFA	--	70(69)	22(18)	8(13)	8(13)	71(70)	21(17)
	DMSO-$\underline{d}_6$	--	72	11	17	7	71	22
6	$CDCl_3$	--	68	25	7	20	69	11
	"	0.5:1	5	74	21	73	20	7
	"	2.0:1	4	73	23	73	18	9
	"	3.0:1	14	66	20	64	26	10
	TFA	--	52(54)	40(34)	8(12)	28(30)	59(55)	13(15)
	DMSO-$\underline{d}_6$	--	73	21	6	16	74	10

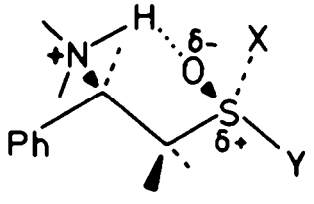
Table 5.- Rotamer populations in $CDCl_3$ (A) and DMSO-$\underline{d}_6$ (B) for the diastereomers of 1 and 1-phenyl-2-methylsulfinylethanol (ref. 16).

Compound	A x_A	x_B	x_C	B x_A	x_B	x_C
Hydroxysulfoxide R^*,R^*	85	3	12	93	7	0
Aminosulfoxide 1α	86	3	11	90	4	6
Hydroxysulfoxide R^*,S^*	83	8	9	56	31	13
Aminosulfoxide 1β	56	30	14	50	41	9

$CDCl_3$, following the procedure described in previous work[3]. The subsequent observation of consistency (or lack thereof) in the variation of conformational populations from one compound to another, taking into account the expected effects to be exerted by the different methyl substitution at nitrogen and by solvent changes, provides a reliable method for checking the correctness of the proton assignment made.

Protonation studies

We have found in previous work that the study of the population changes induced by protonation was particularly useful to asess the conformational preferences of aminothioethers[3]. In the present case, the amino groups are expected to interact in $CDCl_3$ with sulfoxide and sulfone functions by attractive electrostatic ($N^{\delta-}/S^{\delta+}$)[7] and hydrogen bonding (N-H...O-S) or donor-acceptor ($\underline{n}$ -> $\underline{d}$) interactions[1]. Either rotamers A or B will be predominant depending on the relative importance of these interactions compared to steric factors. But whatever this balance may be, when a small amount of TFA is added the effectiviness of the interactions stabilizing A must be diminished since the nitrogen is no longer negatively charged; the electrostatic interaction $N^{\delta+}/S^{\delta+}$ is now repulsive and the donor-acceptor interactions cannot take place. However, new attractive interactions stabilizing rotamer A presumably come into play when the nitrogen is protonated, namely attractive electrostatic interaction $N^{\delta+}/O^{\delta-}$ and/or hydrogen bonding $^{+}$N-H...O-S (Figure 2).



X,Y = :,Me

Figure 2.- Electrostatic interactions in the protonated aminosulfoxides.

Nevertheless, the trifluoracetate ion must be adequately solvated (or free of tight gegenion pairing) for these interactions to be effective[8] and, as we found in previous work[3], this is not the case when the TFA:substrate molar ratio is less or equal to one. Therefore, whatever the original preference in $CDCl_3$ may be, a diminution of x_A should take place with the initial addition of TFA. It

may be seen in the Tables that this expected behavior is observed when one takes solution 1 as the correct one in all compounds except 3β, that is to say, if one assumes A to be the preferred rotamer in $CDCl_3$ for all cases but 3β [9].

A detailed analysis of Tables 2, 3 and 4 also supports the solution taken as correct in each compound: i) if solution 2 were correct for sulfoxides 1α and 2α (Table 2) and sulfones 4 and 5 (Table 4), steric factors would have to be paramount in controlling conformational equilibria since rotamer B would then be assumed to be predominant. However, it can be observed in Tables 2 and 4 that solution 2 gives a higher x_C population, regardless of solvent, compared to that of rotamer A[10], which is not reasonable at all since C is by far the most sterically crowded rotamer (Fig. 1). Solution 1 is therefore reinforced for 1α, 2α, 4 and 5; ii) if rotamer B were predominant in pure TFA for the sulfoxides (solution 2 of Table 2), steric repulsion between the heteroatomic functions would have to override any possible electrostatic attraction between them. This hypothesis conflicts with the observed trend of x_B in solution 2 in pure TFA (Table 2) in the series 1α(76%), 2α(63%), 3α(45%), which is in the opposite sense to that expected based on the increasing size of the respective ammonium functions [$^{+}NH_3$(1α) < $^{+}NH_2Me$(2α) < $^{+}NHMe_2$(3α)]. The same rationale can be applied to the sulfones 4, 5 and 6 (see Table 4, solution 2) and to sulfoxides 1β and 2β (see Table 3, solution 2). On the other hand, if one accepts solution 1, the observed change in x_A in pure TFA on going down the Tables agrees with the expected increase of size of the ammonium function [Table 2: x_A=77%(1α) > x_A=72%(2α) > x_A=42%(3α); Table 3: x_A=61%(1β) > x_A=48%(1β); Table 4: x_A=83%(4) > x_A=70%(5) > x_A=52%(6)]; iii) it appears that 3β is the only case where rotamer B (Fig. 1) is predominant (see above). Now the amino group in 3β is the bulkiest in its homologous series and this compound should therefore display a lower x_A value than 1β or 2β. If solution 1 is correct for the latter compounds as it is suggested by the above evidence, only solution 2 for 3β complies with this rationale, regardless of solvent (see Table 3).

Configurational assignment of sulfoxides

Once a reasonable basis for conformational analysis and proton assignment had been developed, one can asses which epimeric sulfoxide, α or β, is R^*,R^* and which R^*,S^*. It is seen in Tables 2 and 3 that, for a given sulfoxide in $CDCl_3$, rotamer A is at least 30% more populated (at the expense of B, which is correspondingly at least 30% less populated) in the α isomers than in their counterparts. This means that the x_A/x_B ratio -and therefore the relative stability of rotamers A and B- is highly configuration dependent. The configurational assignment may be based on this fact. The most stable A and B

rotamers for the two configurations[11] are depicted in Figure 3.

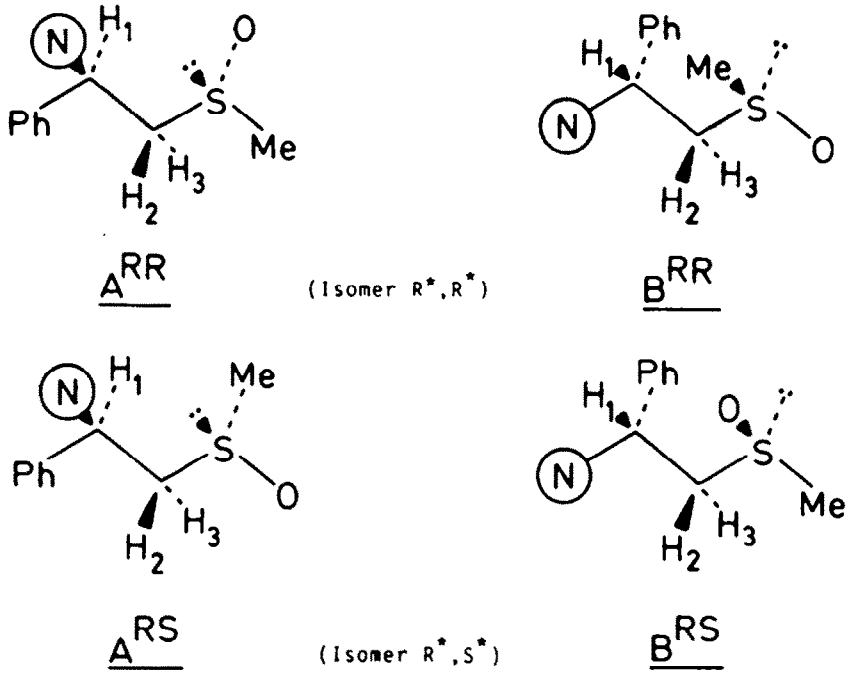


Figure 3.- Most stable conformations (ref. 11) of the sulfoxides under study.

Dealing first with the B rotamers, it may be observed (Fig. 3) that B^{RS} should be more stable than B^{RR} since the former has a $(O/H)_{1,3-p}$ interaction (perhaps stabilizing if one recalls the slight axial preference of S-O group in thiane S-oxide[12]) and the latter a destabilizing $(Me/H)_{1,3-p}$ steric interaction. The same rationale may be applied to A^{RS} and A^{RR}; in the latter, the n -> d donor-acceptor interaction[1] might be also a contributing stabilizing factor[13]. This analysis, then, suggests that the R*,R* isomers should display a higher x_A/x_B ratio than their R*,S* epimers. Therefore, one should assign the R*,R* configuration to the α and the R*,S* configuration to the β isomers.

It is interesting to compare the results obtained for both isomers of 1 and the diastereomeric 1-phenyl-2-methylsulfinylethanol[16] (see Table 5) where the proton assignment was unequivocal from additional data (i.e. long range H-O-C-C-H coupling constants[16]) and the configurational assignment was confirmed by X-ray diffraction analysis[16]. It may be observed in Table 5 that the behavior of 1 α and the hydroxysulfoxide of configuration R*,R* is almost identical regardless of the solvent, supporting the previous configurational assignment[17]

and suggesting that the stability of A rotamer is not altered by the replacement of the heteroatomic function (OH by NH_2) in position 2. In contrast, the behavior of 1β in $CDCl_3$ deviates from that of the corresponding hydroxysulfoxide R*,S*. In the case of the R*,S* hydroxysulfoxide intramolecular hydrogen bonding was an important stabilizing factor of rotamer A[18] whereas in 1β this factor hardly contributes to the stabilization of that rotamer (vide infra). When intramolecular hydrogen bonding is not possible, as in DMSO-$\underline{d}_6$, the populations of both hydroxy- and aminosulfoxides are in reasonable agreement (Table 5), again reinforcing the previous configurational assignment.

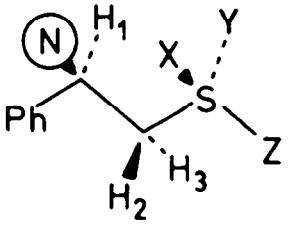
DISCUSSION

The aminosulfoxides studied in this work exhibited substantial differences in conformational behavior (vide supra) similar to those displayed by their homologous β-oxygenated derivatives[1] or even larger, as in the case of the 3α /3β pair (see Tables 2 and 3). The response toward solvent polarity changes resulted also configuration dependent. It may be seen in Table 3 that x_B slightly increases in isomers 1β and 2β at the expense of x_A and x_C as solvent polarity increases (from $CDCl_3$ to DMSO-$\underline{d}_6$). This fact suggests a slight contribution from intramolecular hydrogen bonding and/or electrostatic $\delta^-_N/\ \delta^+_S$ attraction to the stability of the conformations with the heteroatomic functions in gauche arrangement (Fig. 1) in the β sulfoxides (R*,S*). However, a similar population change is observed in 3β, where hydrogen bonding is not possible to begin with, and the contribution of even a weak intramolecular association in 1β and 2β should therefore be disregarded. On the other hand, neither electrostatic $\delta^-_N/\ \delta^+_S$ attraction nor steric factors should be important in controlling the equilibria of α isomers (Table 2) since i) x_A is almost unaltered by the increase in solvent polarity and ii) these compounds, in $CDCl_3$ or DMSO-$\underline{d}_6$, showed a remarkable insensitivity toward increasing methyl substitution at nitrogen [in contrast to what is observed in their β epimers (Table 3) and sulfones (Table 4) where x_A decreases on going down the Tables, i.e. according to the increasing size of amine function]. These findings strongly suggest a special stability of A rotamer in α isomers that may be explained in terms of the n -> d donor acceptor interaction proposed in β-oxygenated sulfoxides[1], between the lone pair of nitrogen and properly oriented d orbital at sulfur. This interaction can be attained in a conformation similar to A^{RR} (Fig. 3)[11] but not in A^{RS}.

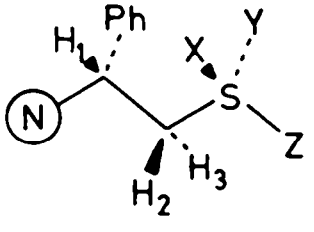
Among the conformational behavior differences exhibited by the aminosulfoxides studied in this work, those related with protonation resulted specially interesting. When the nitrogen is protonated, the electrostatic attraction $\delta^+_N/\ \delta^-_{O\text{-}S}$ (Fig. 2) should play a significant role in the

stabilization of A rotamer. This hipothesis is supported by the observed increase of x_A from $CDCl_3$ to high TFA:substrate molar ratios in sulfoxide 1β (Table 3) and sulfone 4 (Table 4)[20,21]. However, the population of A rotamer in the α sulfoxides is higher in $CDCl_3$ than in any TFA/$CDCl_3$ mixture or pure TFA (Table 2), suggesting that the interaction of ^+N with SO in the α isomers (R^*,R^*) is less favorable than that of the free amine with sulfoxide group. This finding might constitute the first experimental evidence concerning the high importance of the n -> d donor-acceptor interaction[22] in adequately oriented β-heteroatomic sulfoxides[1]. Unfortunately, the semiquantitative character of this work does not allow estimation of the magnitude of this stabilization[23].

Finally, the sulfones 4-6 showed almost no change with medium polarity suggesting that the electrostatic component of the interactions between the nitrogen and sulfone functions does not play a significant role in controlling the conformational equilibria of β-aminosulfones, in contrast to what was observed in homologous β-oxigenated sulfones[7]. The high contribution of rotamer A in compounds 4-6 should be attributed to the instability of conformation B rather than to any special stabilization of A since it is seen in Fig. 4 that, whatever be the arrangement around the C-S bond in rotamer B, there is always an unfavorable 1,3-parallel interaction between the phenyl group and the oxygen or methyl groups of the sulfone.



Rotamer	X	Y	Z
A_1	O	O	Me
A_2	O	Me	O
A_3	Me	O	O



Rotamer	X	Y	Z
B_1	O	O	Me
B_2	O	Me	O
B_3	Me	O	O

Figure 4.- Conformations A and B of sulfones studied in this work.

Long range coupling constants have been observed between the methyl hydrogens of the sulfone and the methylene group (see Table 1). In sulfones 4 and 5 the methyl is equally coupled with both methylene protons (^4J = 0.6 Hz) suggesting either free rotation around the C-S bonds or approximately equal populations for the rotamers A_2 and A_3 of Fig. 4 [which can display a "W" arrangement between one of the methyl hydrogens and H(2) or H(3), respectively]. However, the dimethylamino sulfone 6 displays two different long range couplings, 0.95 Hz and 0.5 Hz (Table 1), the methylenic proton that shows the lowest vicinal coupling with H(1) -and should be therefore in gauche relationship to H(1)- having the highest long range coupling with the methylsulfonyl hydrogens. This inequality of the long range couplings strongly suggests that when the nitrogen function is dimethylamino, the C-S bond is predominantly arranged as shown in rotamer A_3 of Fig. 4[24]. A similar situation has been also found in β-alkoxysulfones[25,26]. It appears that the C-S bond rotation is only severe limited when the adjacent heteroatomic function (O-alkyl or NMe_2) does not bear any hydrogen, the methyl attached to sulfur being forced to an 1,3-parallel relationship with nitrogen (or oxygen in β-oxygenated sulfones). This arrangement is probably attained to overcome the repulsion between the lone pairs of the β heteroatom and the sulfonyl oxygen that otherwise would take place[27].

EXPERIMENTAL PART

Melting points were determined on a Buchi 594392 type S apparatus in open capilary tubes and are uncorrected. Elemental analyses were performed by the "Instituto de Química Orgánica del CSIC" in Madrid with a Perkin-Elmer 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. Proton nmr spectra were recorded in the FT mode on a Varian XL-100-15 spectrometer coupled with a Varian 620/L 16K computer transforming 8K 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 LAOCOON3 program[28] on a VAX 11/780 computer. We estimate the reliability of all values to be within 0.1 Hz; the root mean square deviations for the calculated and experimental lines were always better than 0.05 Hz.

1-phenyl-2-methylsulfinylethylamine (1) was obtained by oxidization of 1-phenyl-2-methylthioethylamine[29] with one equivalent of sodium metaperiodate or m-chloroperoxybenzoic acid following described procedures[29,30]; yield 85-90%. Separation of the diastereomer designated α was carried out by repeated crystallization from benzene; m.p. 115-117°C. The other isomer (β) was recovered from the mother liquors and recrystallized from ethyl ether; m.p. 70-72°C. MS m/e(relative intensity) 1α 120(37), 119(53), 107(8), 106(100), 104(37), 103(34), 91(19), 79(34), 78(12), 77(41), 63(11); 1β 120(40), 119(57), 107(10), 106(100), 104(42), 103(39), 91(23), 79(39), 78(16), 77(48), 63(15). ^{1}H-nmr 1α ($CDCl_3$) δ 2.12 (s broad, NH_2), 2.59 (s, CH_3S), 2.95 (m, CH_2S), 4.59 (m, CHN), 7.26 (m, arom.); 1β ($CDCl_3$) δ 2.24 (s broad, NH_2), 2.59 (s, CH_3S), 3.00 (m, CH_2S), 4.54 (m, CHN), 7.35 (m, arom.). IR mixture of diastereomers (KBr) 3460, 3370, 2910, 1605, 1495, 1455, 1023, 795, 765 and 705 cm^{-1}. **Picrate** of 1α, m.p. 176-178°C. **Picrate** of 1β, m.p. 230-238°C; anal. calculated for $C_{15}H_{16}O_8N_4S$, C 43.7, H 3.9, N 13.6, S 7.8; found (mixture of diastereomers) C 43.8, H 3.9, N 13.6, S 7.6.

N-methyl-1-phenyl-2-methylsulfinylethylamine (2) was obtained from N-methyl-1-phenyl-2-methylthioethylamine[29] following identical procedures to those indicated for 1; yield 80-85%. The diastereomers could not be separated by crystallization. MS m/e(relative intensity) 134(20), 133(80), 132(90), 121(9), 120(100), 119(25), 118(33), 91(26), 78(15), 77(29), 63(10), 42(70). ^{1}H-nmr ($CDCl_3$) δ 1.78 (s broad, NH), 2.09 (s broad, NH), 2.29 (s, CH_3N), 2.32 (s, CH_3N), 2.56 (s, CH_3S), 2.59 (s, CH_3S), 2.94 (m, CH_2S α isomer), 2.98 (m, CH_2S

β isomer), 4.07 (m, CHN α isomer), 4.13 (m, CHN β isomer), 7.35 (m, arom.). IR (film) 3460, 3340, 2810, 1495, 1455, 1310, 1140, 1030, 765 and 700 cm^{-1}. **Picrates.**- The diastereomeric picrates could be partially separated in bad yield after repeated crystallization from ethanol. The precipitated mixture is 75% enriched in one isomer and its epimer could be recovered from the mother liquors in 70% excess. Treatment of these mixtures with aqueous sodium bicarbonate followed by extraction and work-up yielded analytical samples of each enriched diastereomer; m.p. mixture of diastereomers 130-140°C. Anal. calculated for $C_{16}H_{18}O_8N_4S$, C 45.1, H 4.3, N 13.1, S 7.5; found C 45.2, H 4.5, N 13.1, S 7.6.

N,N-dimethyl-1-phenyl-2-methylsulfinylethylamine (3).- Method a) Fifty milliliter of 50% aqueous dimethylamine solution and 1.54 g (0.01 mol) of β-methylsulfinylstyrene in 20 ml of ethanol were stirred at room temperature for 30 days. The solvent was removed and the mixture treated with 50 ml of 20% hydrochloric acid and extracted several times with methylene chloride to remove non-basic impurities. The aqueous layer was carefully neutralized with 20% sodium hydroxide and extracted with methylene chloride. Work-up of the extracts yielded 1.83 g (92%) of the two diastereomers that could not be separated in our hands. Method b) To 0.2 g (1.2 mmol) of 1α or 1β 0.18 g (3.6 mmol) of 88% formic acid and 0.27 g (3.6 mmol) of commercial 40% formaldehyde were added at 0°C and the mixture stirred at 80°C for 24 h. Dilute hydrochloric acid (1 ml) was added at room temperature and the mixture was extracted with methylene chloride to remove non-basic impurities and then neutralized with diluted sodium hydroxide. Extraction of the aqueous layer with methylene chloride and usual work-up yielded 0.15-0.20 g of 3α or 3β, depending on the starting material. The product did not crystallize. Method c) To a solution of 0.2 g (1.2 mmol) of 1α or 1β in 5 ml of methanol 1 g (13 mmol) of commercial 40% formaldehyde were added and the mixture refluxed for 2 h. Sodium borohydride (0.6 g; 16 mmol) was added at room temperature and the mixture stirred overnight. Solvent was removed and the residue extracted with methylene chloride. Work-up of the extracts yielded a mixture of the α or β isomers, depending on the starting material, of 1, 2 and 3 whose configurations were thereby chemically correlated. MS mixture of diastereomers m/e(relative intensity) 148(11), 147(62), 146(100), 134(60), 105(12), 104(23), 103(15), 91(25), 78(11), 77(20). ^{1}H-nmr 3α ($CDCl_3$)δ 2.26 (s, $(CH_3)_2N$), 2.64 (s, CH_3), 3.21 (m, CH_2S), 4.14 (m, CHN), 7.30 (m, arom.); 3β ($CDCl_3$) δ 2.34 (s, $(CH_3)_2N$), 2.68 (s, CH_3S), 3.30 (m, CH_2S), 3.93 (m, CHN), 7.30 (m, arom.). IR mixture of diastereomers (film) 2960, 2800, 1460, 1040, 750 and 700 cm^{-1}. **Picrates**, m.p. mixture of diastereomers 170-175°C. Anal. calculated for $C_{17}H_{20}O_8N_4S$ C 46.4, H 4.5, N 12.7, S 7.3; found C 46.1, H 4.3, N 12.6, S 7.5.

N-phenyl-2-methylsulfonylethylamine (4).- It was synthetized in 65% yield by oxidization of 1-phenyl-2-methylthioethylamine[3] with two equivalents of sodium metaperiodate following described procedures[29] and purified by recrystallization from carbon tetrachloride; m.p. 63-66°C. MS m/e(relative intensity) 120(9), 119(53), 107(9), 106(100), 104(29), 91(9), 79(30), 77(20). ^{1}H-nmr ($CDCl_3$)δ 1.90 (s broad, NH_2), 2.93 (s, CH_3S), 3.30 (m, CH_2S), 4.64 (m, CHN), 7.35 (m, arom.). IR (nujol) 3395, 3300, 3230, 1610, 1505, 1300, 1140, 1105, 910, 810, 780, 720 and 705 cm^{-1}. **Picrate** m.p. 158°C (dec.). Anal. calculated for $C_{15}H_{16}O_9N_4S$ C 42.1, H 3.8, N 13.1, S 7.5; found C 42.1, H 3.6, N 13.3, S 7.8.

N-methyl-1-phenyl-2-methylsulfonylethylamine (5).- It was prepared in 69% yield by oxidization of N-methyl-1-phenyl-2-methylthioethylamine[3] following the identical procedure to that indicated for 4 and recrystallized from carbon tetrachloride; m.p. 76-78°C. MS m/e(relative intensity) 133(27), 132(36), 121(9), 120(100), 118(7), 104(14), 91(9), 79(3), 78(9), 77(14), 57(12), 42(43). ^{1}H-nmr ($CDCl_3$) δ 1.89 (s broad, NH), 2.28 (s, CH_3N), 2.86 (m, CH_3S), 3.29 (m, CH_2S), 4.17 (m, CHN), 7.38 (m, arom.). IR (KBr) 3500, 3355, 2810, 1310, 1287, 1260, 1150, 1140, 1110, 965, 870, 740 and 705 cm^{-1}. Anal. calculated for $C_{10}H_{15}O_2NS$ C 56.3, H 7.1, N 6.5; found C 56.0, H 7.3, N 6.2.

N,N-dimethyl-1-phenyl-2-methylsulfonylethylamine (6).- It was obtained in 86% yield from dimethylamine and β-methylsulfonylstyrene following identical procedure to that described for 3 (Method a); m.p. 64-67°C. MS m/e(relative intensity) 227(3) M$^+$, 147(14), 146(26), 135(17), 134(100), 104(17), 102(20), 91(18), 78(12), 77(21). ^{1}H-nmr ($CDCl_3$) δ 2.17 (s, $(CH_3)_2N$), 2.84 (m, CH_3S), 3.48 (m, CH_2S), 4.20 (m, CHN), 7.27 (m, arom.). IR (nujol) 3030, 2890, 2855, 2810, 1310, 1160, 1130, 1095, 1055, 1010, 975, 915, 860, 780, 760, 740 and 710 cm^{-1}. **Picrate**, m.p. 180-185°C. Anal. calculated for $C_{17}H_{20}O_9N_4S$ C 44.7, H 4.4, N 12.3, S 7.0; found C 44.6, H 4.5, N 12.3, S 7.3.

ACKNOWLEDGEMENT. We are indebted to Prof. Ernest L. Eliel for discussing the manuscript and for his improvement of our "broken" english.

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8.- The protonation of oxygen of sulfoxide and sulfone funtions by TFA is a complicating factor that cannot be a priori dismissed. We have observed, in similar compounds, that this factor is negligible at least at TFA:substrate ratios lower than ca. 2 (see ref 2). In any case, protonation of sulfinyl or sulfonyl oxygens would prevent these atoms from interacting favorably with protonated nitrogen by the proposed electrostatic and/or hydrogen bonding interactions.

9.- It should be noted that, to calculate the populations (see ref. 6), we have used an electronegativity value for nitrogen increased by 0.5 units when this atom is protonated, i.e. for TFA:substrate molar ratios greater than one. The influence of this change on the population values is illustrated for each compound of Tables 2, 3 and 4 by the two sets of values placed in the pure TFA entries (values in parenthesis calculated with normal nitrogen electronegativity). It may be seen that this electronegativity change induces a variation in populations that, in our view, does not materially affect the semiquantitative conclusions of this work.

10.- We believe that the differences between x_C and x_A are in general too high to be attributable simply to errors in population calculations due to poor assesment of either substituent electronegativity (see ref. 6) or dihedral angle deformations (see ref. 3).

11.- Those rotamers around the C-S bond that contain 1,3-parallel (1,3-p) interactions between second row elements have been excluded. There are two conformers among them, one for each configuration, where intramolecular hydrogen bonding N-H...O-S could be postulated. Experimental evidence (vide infra) has shown the unimportance of this interaction in these compounds and these rotamers have been also omitted in Fig. 3. C rotamers (Fig. 1) are not considered due to their low conformational populations in the compounds under study (cf. Tables 2 and 3).

12.- J.B. Lambert and R.G. Keske, J. Org. Chem., 1966, 31, 3429.

13.- It might be argued that the repulsion between the lone pairs of nitrogen and sulfur in rotamers A of Fig. 3 could play a destabilizing role in similar fashion to that observed in previous cases (see refs. 3 and 14). Nevertheless, the electrostriction and/or increased s character of the sulfur orbital (see ref. 15), as well as the electrostatic N/S attraction (see ref. 8), should outweigh this unfavorable effect.

14.- N.S. Zefirov, G.L. Gurvich, A.S. Sashkov, M.Z. Krimer and E.A. Vorob'eva, Tetrahedron, 1976, 32, 1211.

15.- R.O. Day, C.A. Kingsbury and V.W. Day, J. Org. Chem., 1981, 46, 1004.

16.- F. Alcudia, E. Brunet, J.L. Garcia Ruano, M.A. Hoyos, P.Prados and J.H. Rodriguez, Org. Magn. Reson., 1984, 21, 643.

17.- It should be stressed at this point that the simple melting point criterion established in previous work (see ref 1) to assign configuration of β-hydroxysulfoxides appears to be applicable also to the β-aminosulfoxides since in the case of 1 and in the corresponding N-phenylderivative (see ref. 2), the α isomer melts at higher temperature than its epimer .

18.- This situation is similar to that found in cis-3-hydroxythiane S-oxide (see ref. 19) (R ,S configuration) where at moderate dilution the equilibrium lies almost entirely to the intramolecularly hydrogen bonded diaxial conformation.

19.- E.L. Eliel and E. Brunet, Tetrahedron lett., 1985, 3421.

20.- It may be observed that in the protonation of NH_2 and NHMe derivatives, the maximum x_A value is attained at TFA:substrate molar ratios of 3-5 rather than in pure TFA, suggesting that the higher polarity of pure TFA compared to $CDCl_3$/TFA mixtures minimizes the electrostatic +N/ δ-O-S attraction (cf. Fig 2) that comes into play when the nitrogen is protonated, provided a relatively excess of TFA is present to solvate the anion (see ref. 3).

21.- The methylamino derivatives 2β and 5 displayed almost equal x_A values in $CDCl_3$ and high TFA:substrate molar ratios. In these compounds, the aforementioned electrostatic attraction (Fig. 2) is presumably attenuated by delocalization of positive charge on the methyl of $+NH_2Me$ group and by the bigger size of this function compared to $+NH_3$. In the dimethylamino derivatives 3β (Table 3) and 6 (Table 4) rotamer A is less populated in TFA than in $CDCl_3$ and, at the same time, the observed changes of x_A upon gradual addition of TFA are greater than in any other of the compounds studied, reflecting the higher steric demand of the $+NHMe_2$ group compared to the less methylated ammonium functions.

22.- This is so provided the B rotamer does not change its stability with protonation. It may be seen in Fig. 3 that protonation of B rotamers should not induce severe steric changes in them.

23.- We have observed that the conformational equilibria of 3-methylsulfinyloxanes (F. Alcudia et al., unpublished results) is also configuration dependent. This result is very significant concerning the existence of the n -> d donor acceptor interaction since, if the relative configuration of these compounds is accurately determined, it should provide conclusive evidence as to the importance of such interaction in -heterosubstituted sulfoxides. Work is proceeding.

24.- It should be noted that if B were predominant in the case of 6, the preferred arrangement of heteroatoms in view of the unequality of long range couplings would be that of B_2 [methyl bound to sulfur in anti arrangement to the methylenic proton in gauche relationship to H(1); Fig. 4]. This is not reasonable at all since this is the least stable B rotamer (contains a strongly destabilizing Me/Ph 1,3-parallel interaction; Fig. 4) and the predominance of A rotamer in the conformational equilibrium of 6 is therefore specially reinforced.

25.- F. Alcudia, J.L. Garcia Ruano, J.G. Arribas, P.Prados and J.H. Rodriguez, An. Quim., 1982, 78C, 190.

26.- F. Alcudia and E.L. Eliel, J. Am. Chem. Soc., 1974, 96, 1939.

27.- Other authors have proposed in similar compounds an attractive interaction between the methyl of $MeSO_2$ group (on which the positive charge of sulfur is delocalized) and the β-heteroatom (see ref. 7). Which is the correct explanation is not certain. However, the fact that the long range coupling constants did not change with increasing medium polarity (see Table 1), i.e. the rotamer population around the C-S bond was unaffected by polarity changes, might be taken as evidence against a purely electrostatic SO_2Me/N attraction (which should be attenuated in the more polar solvent DMSO-d_6).

28.- S.M. Castellano, "LAOCN3 in Computer Programs for Chemistry" vol. 1, p 10, ed. D.F. Datar, Benjamin, New York 1968.

29.- M.J. Leonard and H.W. Johnson jr., J. Org. Chem., 1962, 27, 282.

30.- M. Fieser, "Reagents for Organic Synthesis" vol. 11, p 122, John Wiley & Sons 1984, and references therein.