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Synthesis and Conformational Study of β−Hydroxy Sulfones, Bioisosteres of Oxisuran Metabolites, and Their *O*-Methyl Derivatives.

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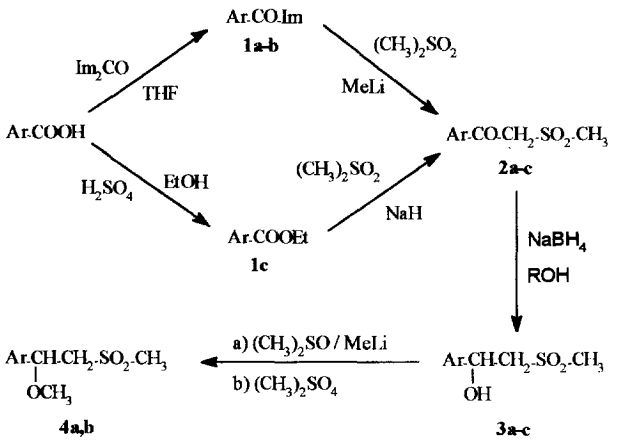
Abstract: The synthesis and conformational analysis of 2-(methylsulfonyl)-1-(2-quinolyl)ethanol, 2-(methylsulfonyl)-1-(1-isoquinolyl)ethanol, 2-(methylsulfonyl)-1-(2-pyrazinyl)ethanol, and the *O*-methyl derivatives, 2-(methylsulfonyl)-1-(methoxy)-1-(2-quinolyl)ethane and 2-(methylsulfonyl)-1-(methoxy)-1-(1-isoquinolyl)ethane, are reported. The conformational analysis of β-hydroxy sulfones and β-methoxy sulfones has been carried out from the observed vicinal coupling constants, using a molecular mechanics force field (MMX) and the Altona relationship as fundamental tools. Polar interactions are the main factor that control the stability of the different conformations being the steric effects and intramolecular hydrogen bonding less important contributions.

Oxisuran (2-(methylsulfinyl)-1-(1-pyridyl)ethanone) and its metabolites are immunosuppressive agents which reportedly have the unique property of inhibiting cell-mediated immunity without any concomitant elimination of humoral antibody formation.[1] These compounds have sparked the study of several series of bioisosteres incorporating different heterocyclic systems.[2] In many cases, the latter are less toxic than oxisuran and may be used as immunosuppressors. Despite the interest in these drugs, little is understood of their mechanism of action or the drug-receptor interactions. In order to elucidate the relationships between the structure and the associated pharmacological properties of these compounds, we have reported previously the conformational analysis of some bioisosteres of oxisuran metabolites: β-hydroxy sulfoxides and their *O*-methyl derivatives.[3] For such compounds the conformational equilibrium was explained in terms of polar and steric factors and, in some cases, intramolecular hydrogen bonding was significatively important.

In the present paper, we report the synthesis and conformational analysis of the corresponding β-hydroxy sulfones and their *O*-methyl derivatives (Scheme 1).



Ar= **a:** 2-quinolyl; **b:** 1-isoquinolyl; **c:** 2-pyrazinyl.
Im= 1-imidazolyl.
R= methyl; ethyl.

Scheme 1

RESULTS AND DISCUSSION

Synthesis

The synthetic pathways used for preparation of compounds **1-3(a,b,c)** and **4(a,b)** are shown in Scheme 1.

β-Oxo sulfones **2a** and **2b** were synthesized following the method we have reported previously.[4] By the same procedure, the synthesis of sulfone **2c** was unsuccessful probably due to the low solubility of pyrazinic acid in THF that prevents formation of the imidazolide derivative. Initially, compound **2c** was prepared by acylation of lithium (methylsulfonyl)methylide with 2-ethoxycarbonylpyrazine **1c** by the same procedure described for the synthesis of the corresponding β-oxo sulfoxide.[3] However, this method lead to β-oxo sulfone **2c** in low yield. Moreover, the presence of dimethylsulfone made it difficult to isolate the pure product. Reaction of **1c** with sodium (methylsulfonyl)methylide to form the sulfone **2c** proved to be a much more satisfactory procedure. Attempts to oxidize the sulfoxide function of 2-(methylsulfinyl)-1-(2-pyrazinyl)ethanone by general procedures[5] were not successful.

The reduction of the carbonyl group of compounds **2a-c** with sodium borohydride yielded β-hydroxy sulfones **3a-c** without any observable cleavage of the carbon-sulfur bond.

Hydroxy sulfones **3a,b** were methylated to afford the corresponding methoxy sulfones **4a,b** in good yields; alkylation proceeded by reaction with dimethyl sulfate in the presence of lithium (methylsulfinyl)methylide as base. By this method we have prevented the formation of dehydration product that is usual in another basic media.

Conformational analysis

The conformational analysis of **3a-c** and **4a,b** has been carried out from the experimentally observed vicinal coupling constants ($J_{1,2}$ and $J_{1,3}$), using a molecular mechanics force field[6] (MMX derived from MMP2)[7] as the fundamental tool, following the same method that we have employed previously for the corresponding sulfoxides.[3] The validity of this method has been tested studying monoconformational compounds.[8]

The staggered conformations around the CH-CH_2 bond of these compounds are shown in Figure 1.

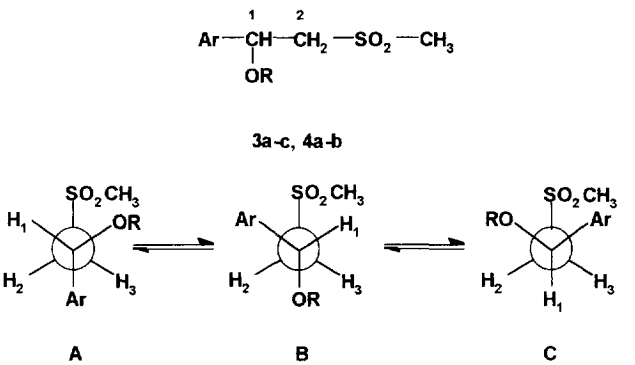


Fig. 1. Staggered conformations resulting from the rotation of the C_1-C_2 bond.

Rotation around the CH_2-S bond gives rise to three different rotamers for each conformer which are designated with the subscripts 1, 2, 3 and collected in Figure 2.

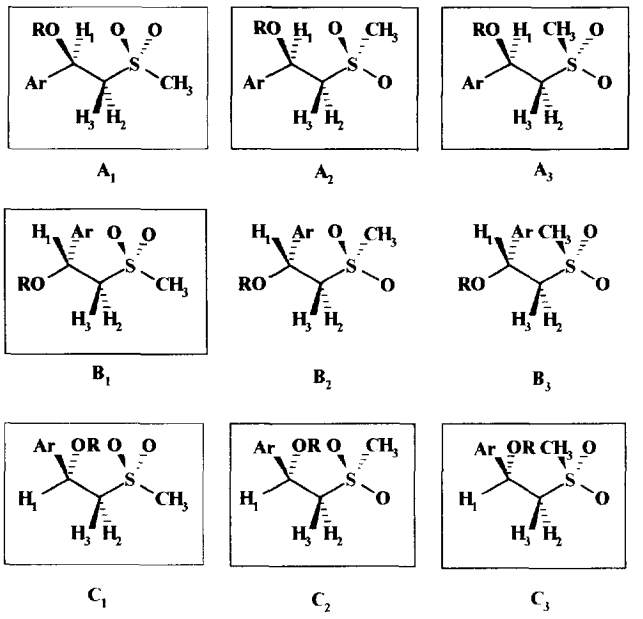


Fig. 2. Staggered rotamers around the C_1-C_2 and C_2-S bonds for sulfones **3a-c** and **4a,b**.

The ^{1}H-NMR parameters of compounds **3a-c** and **4a,b**, which are relevant to the conformational analysis, are collected in Table 1. Other NMR data can be found in the Experimental Section. The spectra were recorded in $CDCl_3$ (or CD_3CN) and DMSO-d_6 in order to test the effect of solvent polarity on the conformational equilibrium.

The sulfones **3a-c** and **4a,b** exhibit a significant difference between the experimental values of the vicinal coupling constants $J_{1,2}$ and $J_{1,3}$ (Table 1). This fact indicates a marked preference of either rotamer A or B in the conformational equilibria (Figure 1) regardless the polarity of the medium. Therefore, intramolecular hydrogen bonding is not relevant to the conformational equilibria.

Only when the spectra of compounds **3a-c** were recorded in DMSO-d_6, the methylene proton displaying the smallest vicinal coupling with H-1 is also involved in a long-range ^{4}J coupling with the hydroxyl proton (Table 1). It is widely accepted that this ^{4}J coupling is significant only when the protons involved have a *zig-zag* planar arrangement. It is easily seen from Figure 1 that the hydroxyl proton cannot be coplanar with any methylene

Table 1. ^{1}H-NMR Parameters and Conformational Populations of Compounds **3a-c** and **4a-b**

		δ (ppm)						*J* (Hz)			conformer, % [a]			rotamers [b]		
compd	solvent	H_1	H_2	H_3	OH	CH_3	OCH_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	X_A	X_B	X_C	A	B	C
3a	DMSO-d_6 [c]	5.29	3.58	3.74	6.43	3.14	----	2.7	9.9	-14.7	84	12	4	A_3	B_1	C_2
3b	$CDCl_3$ [d]	6.04	3.41	3.28	5.00	3.25	----	1.8	9.9	-15.0	86	4	10	A_3 [e]	B_1 [e]	C_2 [e]
	DMSO-d_6 [f]	6.29	3.66	3.96	5.88	3.15	----	3.0	9.0	-15.0	72	12	16	A_3	B_1	C_2
3c	CD_3CN [g]	5.32	3.46	3.57	4.37	3.04	----	3.0	9.3	-15.0	74	11	15	A_3	B_1	C_1 [h]
	DMSO-d_6 [i]	5.20	3.47	3.70	6.41	3.10	----	2.7	9.3	-14.7	76	6	18	A_3	B_1	C_2
4a	$CDCl_3$ [j]	5.10	3.39	3.66	----	3.12	3.44	2.4	10.2	-15.3	88	8	4	A_3	B_1	C_2
	DMSO-d_6	5.04	3.55	3.98	----	3.13	3.33	2.5	10.0	-15.0	85	9	6	A_3	B_1	C_2
4b	DMSO-d_6	5.60	3.70	4.18	----	3.15	3.21	3.3	9.0	-15.0	73	18	9	A_3	B_1	C_2

[a] Calculated conformational populations. [b] Selected rotamers for calculation of the conformational populations. [c] $^3J_{H_1,OH}$ = 5.4 Hz; $^4J_{H_2,OH}$ = 1.5 Hz. [d] $^4J_{H_2,Me}$ = 1.5 Hz. [e] Intramolecular hydrogen bonding with the nitrogen of the aromatic ring. [f] $^4J_{H_2,OH}$ = 0.9 Hz. [g] $^4J_{H_2,Me}$ = 1.2 Hz. [h] Intramolecular hydrogen bonding with the sulfonyl group. [i] $^4J_{H_2,OH}$ = 1.2 Hz. [j] $^4J_{H_2,Me}$ = 1.2 Hz.

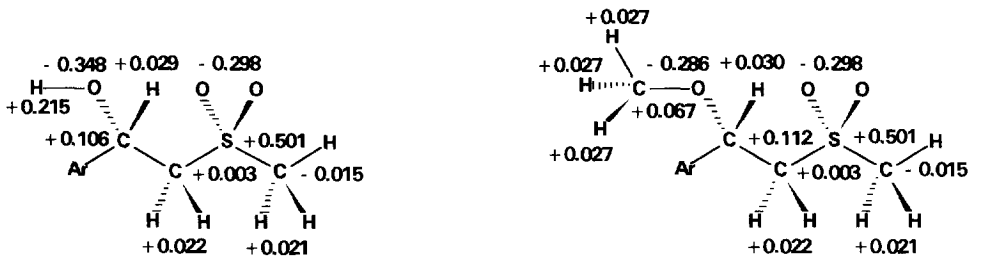
proton in conformation B; therefore, rotamer A predominates in the equilibrium. This fact has led us to the unequivocal assignment of protons H-2 and H-3 of Figure 1 to the spectrum signals.

On the other hand, a long-range coupling constant (^4J) is observed between protons of the methylsulfonyl group and the methylene proton displaying the smallest vicinal coupling with H-1 (Table 1). This ^4J coupling constant indicates that A_3 is the preferred rotamer around the C_2-S bond (Figure 2) because this is the only one type A rotamer that exhibits the required *zig-zag* planar arrangement between the involved protons. Predominance of the rotamer A_3 can be justified due to the high value of the $^4J_{H\text{-}2,Me}$ constant (1.2-1.5 Hz).

The preference for conformation A may be rationalized by considering both steric effects and electrostatic interactions between heteroatoms. The positive partial charge on the sulfur atom of the sulfones points out to strong electrostatic interactions with the hydroxyl oxygen. This interaction will essentially contribute to enhance the stability of conformations A and C, compared with rotamers of type B, while steric effects may account for the nil or very small contribution of conformation C to the overall equilibrium.

Assuming a predominance of type A conformer, the conformational equilibrium around the C_2-S bond (Figure 2) is shifted towards rotamer A_3 in spite of the existing steric interactions. This conformational preference cannot be explained by invoking a predominant role of polar *gauche* interactions. However, it may be justified by considering *1,3-parallel* interactions between groups.

The residual charges on the atoms of compounds **3a-c** and **4a-b**, expressed as a fraction of the elemental electric charge, were calculated with the RESCHA computer program[9] (Figure 3).



Calculated charges on aromatic carbon and heterocyclic nitrogens of compounds **3a-c** and **4a,b**.

Compound	**3a**	**3b**	**3c**	**4a**	**4b**
C_{Ar}	+0.067	+0.067	+0.068	+0.067	+0.067
N	-0.199	-0.200	-0.148[a] -0.153[b]	-0.199	-0.200

[a] On nitrogen number 1. [b] On nitrogen number 4.

Fig. 3. Residual charges (fraction of elemental electric charge) of the atoms for compounds **3a-c,** and **4a,b**.

As depicted in Figure 3, although the carbon atom of the methyl group is σ-rich, the $(Me/OR)_{1,3-p}$ interaction is less repulsive than the $(O/OR)_{1,3-p}$. Taking into account these destabilizing interactions computed for type A rotamers, conformer A_3 has to be more stable than the rotamers A_1 and A_2 (Figure 2).

In order to choose the significant conformers, the energy of polar interactions should be considered since such interactions play an important role on the conformational equilibria of these compounds. The energy of polar interactions can be estimated from the model proposed by Zefirov,[10] the residual charges on the involved atoms calculated from the RESCHA program (Figure 3),[9] the distances between groups obtained from the geometrical optimization with the MMX force field[6] (see below), and the equation proposed by Abraham:[11]

$$E_{\mu} = 332\ e_X\ e_Y/r_{X/Y} \quad \text{(kcal/mol)} \qquad (1)$$

where e_X, e_Y are the residual charges on groups X and Y (expressed as a fraction of the elemental electric charge) and $r_{X/Y}$ is the distance (in Å) that separates groups X and Y. The energies of these *gauche* and *1,3-parallel* interactions present in the compounds **3a-c** and **4a,b** are collected in Table 2.

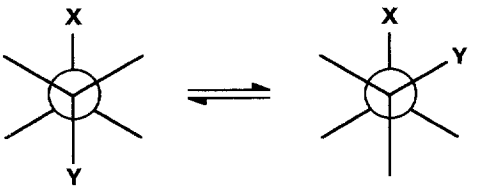
These calculations allow us to conclude that the A rotamer is the preferred one. The contributions of conformations B and C are similar and of small value, taking into account both the steric and polar interactions. As far as the most stable rotamer of each type (A, B and C) is concerned, values of the *1,3-parallel* interactions indicate that rotamers A_3, B_1 and C_2 must predominate (no conclusion can be drawn from the values of *gauche* interactions).

Considering the nine possible conformations collected in Figure 2, the selected conformers (marked with a box) were submitted to a geometry optimization by energy minimization using the molecular mechanics force field (MMX).[6] Rotamers B_2 and B_3 have not been considered according to steric and polar criteria.

There are two possibilities of intramolecular association through hydrogen bonding in compounds **3a-c**: the O-H group with either the sulfonyl oxygen atom (O-H/O-SO) or the heterocyclic nitrogen atom (O-H/N). The latter is only feasible when the former is geometrically hindered and the aromatic ring adopts the suitable spatial arrangement by rotation around the C_{Ar}-C_1 bond. Therefore, the selected conformers (Figure 2) in the β-hydroxy sulfones (**3a-c**) were submitted to geometric optimization with or without intramolecular hydrogen bonding with sulfonyl group or the heterocyclic nitrogen atom. From the results of such energy minimization,

Table 2. Energy of Polar Interactions [a] (kcal/mol) in Compounds **3a-c**, **4a-b**

GAUCHE INTERACTION

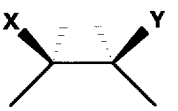


M **N**

$$\Delta E_\mu = E_\mu^N - E_\mu^M$$

X/Y	OH/S	OH/H	OMe/S	OMe/H	S/C-Ar	S/H	C-Ar/H	C-1/O	C-1/Me	O/H	H/Me
$\Delta E\mu$	-3.80	-0.19	-3.12	-0.16	+0.72	+0.14	+0.04	-0.66[b]	-0.03	-0.14	-0.01

1,3-PARALLEL INTERACTION



X/Y	OH/O	OMe/O	OH/Me	OMe/Me	H/O	C-Ar/O	Me/H	C-Ar/Me
$E\mu$	+12.00	+9.86	+0.56	+0.46	-1.03	-2.20	-0.04	-0.09

[a] The energy of polar interactions has been estimated from the model proposed by Zefirov, the residual charges on the involved atoms calculated from the RESCHA computer program, the distances between groups provided by MMX program and the Abraham equation (1). [b] Value for compounds **3a-c**. In the methoxy sulfones **4a** and **4b**, ΔE_μ = -0.69.

the relative energy differences between those conformers with or without intramolecular hydrogen bonding are shown in Table 3. The precise geometry due to these intramolecular associations may involve a higher energy of steric interaction between the different groups and the aromatic ring, depending upon the precise conformation. Therefore, the observed ΔE reflects several energy parameters besides the hydrogen bond term.

Table 3. Relative Energy Differences[a] ($\Delta E = E_i - E_i^*$) between Rotamers with or without Intramolecular Hydrogen Bond

	ΔE (Kcal/mol)						
	OH----O-SO				OH----N		
compd	A_1	A_2	C_1	C_3	A_3	B_1	C_2
3a	0.55	0.93	0.87	0.85	0.42	---[b]	0.88
3b	0.72	---[c]	---[d]	1.27[e]	1.96	0.56	1.64
3c	0.48	0.78	0.88	0.70	---[b]	---[b]	---[b]

[a] Energy minimization differences derived from the molecular mechanics MMX program.[6] [b] Intramolecular hydrogen bond between hydroxyl group and the nitrogen of the aromatic ring is not formed. [c] Calculations using MMX program for the rotamer without hydrogen bonding was not performed. [d] Intramolecular hydrogen bond between hydroxyl group and the nitrogen of the aromatic ring is preferred, ΔE = 1.2. [e] Intramolecular hydrogen bond between hydroxyl group and the nitrogen of the aromatic ring or sulfonyl group are indistinct formed.

Hydrogen bonding to the heterocyclic nitrogen atom (OH/N) is only important in sulfone **3b** (Table 3), since the calculated negative charge on such atom is slightly higher than that in compounds **3a** and **3c** (Figure 3). In this regard, as can be seen in Table 3, the rotamer C_3 is stabilized by both O-H/N and O-H/O_2S associations in sulfone **3b**, and the association O-H/N is the predominant one in the C_1 and A_3 rotamers (*ca* 1.96 kcal/mol in the latter).

From the ΔE values collected in Table 3, it follows that the contribution of intramolecular hydrogen bonding O-H/O_2S to the differential stabilization of rotamers is small in the hydroxy sulfones **3a-c**. This fact agrees with the ^{1}H-NMR experimental data and explains why the most significant type A conformer is A_3 (even though rotamers A_1 and A_2 are stabilized by the hydrogen bond OH/O_2S).

The contribution of the different rotamers to the conformational equilibrium can be estimated using the Equations (2) and (3) :[12]

$$^3J_{ij}^{obs} = \Sigma\, X_n\, ^3J_{ij} \qquad (2)$$

$$\Sigma\, X_n = 1 \qquad (3)$$

The use of these equations with the experimentally observed ^{1}H-^{1}H vicinal coupling constants for the CH-CH_2 rotational system (Table 1), involves a preliminary evaluation of the theoretical coupling constants in rotamers A, B, and C (Figure 1). This evaluation has been carried out by means of the empirical Karplus-type equation (4) proposed by Altona et al.[13] for an ethane fragment with three substituents. Equation (4) relates the ^{1}H-^{1}H vicinal coupling constants to the dihedral angles, the electronegativity of the substituents attached to the rotational system, and their relative orientation with respect to the considered protons:[14]

$$^3J_{ij} = P_1 \cos^2 \phi + P_2 \cos \phi + P_3 + \sum \Delta\chi_i \left[P_4 + P_5 \cos^2 \left(\tau_1 \phi + P_6 \left[\Delta\chi_i\right]\right)\right] \quad (4)$$

The theoretical coupling constants $|^3J_{ij}|$ for all the rotamers considered (Figure 2) were calculated from Equation (4), using the Huggins electronegativities[15] and the dihedral angles obtained from the geometrical optimization. The results have been collected in Tables 4 and 5.

Table 5. Dihedral Angles and Calculated $^3J_{i,j}$ of the Considerate Rotamers for Compounds **4a-b**

compd		rotamers [a]					
		A_1	A_3	B_1	C_1	C_2	C_3
4a	H_1-H_2 [b]	286.55	292.05	181.30	58.83	55.06	62.25
	H_1-H_3 [b]	169.13	174.92	64.16	302.83	299.71	307.47
	$J_{1,2}$ [c]	1.12	1.44	11.56	4.04	4.60	3.56
	$J_{1,3}$ [c]	10.70	11.22	3.51	2.25	1.90	2.83
4b	H_1-H_2 [b]	285.33	289.69	172.90	59.59	61.14	60.70
	H_1-H_3 [b]	167.60	172.39	61.74	303.89	306.31	306.14
	$J_{1,2}$ [c]	1.07	1.28	11.48	3.93	3.71	3.76
	$J_{1,3}$ [c]	10.54	11.02	3.85	2.37	2.67	2.65

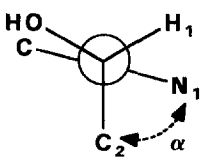
[a] Rotamers submitted to energy minimization. [b] Dihedral angle H-C_1-C_2-H provided by MMX program. [c] Calculated ^{3}J by the Altona equation.[13]

Table 4. Dihedral Angles and Calculated $^3J_{i,j}$ of the Considerate Rotamers for Compounds **3a-c**

compd		rotamers [a]									
		A_1 [b]	A_2 [b]	A_3	A_3 [c]	B_1	B_1 [c]	C_1 [b]	C_2	C_2 [c]	C_3 [b]
3a	H_1-H_2 [d]	295.65	291.41	290.68	290.28	176.64	-----	60.51	56.58	55.63	61.47
	H_1-H_3 [d]	177.77	174.36	173.91	173.54	59.41	-----	303.65	300.92	300.86	305.79
	$J_{1,2}$ [e]	1.73	1.39	1.35	1.32	11.37	-----	3.80	4.38	4.52	3.67
	$J_{1,3}$ [e]	11.41	11.18	11.14	11.11	4.20	-----	2.34	2.03	2.03	2.61
3b	H_1-H_2 [d]	291.75	290.59	292.39	288.61	176.09	177.13	57.75	63.31	62.64	55.24
	H_1-H_3 [d]	173.04	172.65	174.64	171.91	58.95	60.12	301.64	308.01	307.33	300.18
	$J_{1,2}$ [e]	1.42	1.34	1.47	1.22	11.34	11.39	4.20	3.41	3.50	4.58
	$J_{1,3}$ [e]	11.07	11.04	11.20	10.97	4.27	4.09	2.11	2.90	2.81	1.95
3c	H_1-H_2 [d]	294.09	291.98	294.51	-----	175.32	-----	61.00	57.40	-----	59.25
	H_1-H_3 [d]	176.46	174.95	177.55	-----	58.02	-----	304.10	301.64	-----	303.77
	$J_{1,2}$ [e]	1.60	1.44	1.63	-----	11.29	-----	3.73	4.26	-----	3.98
	$J_{1,3}$ [e]	11.33	11.22	11.39	-----	4.41	-----	2.40	2.11	-----	2.36

[a] Rotamers submitted to energy minimization. [b] Intramolecular hydrogen bond between hydroxylic and sulfonyl groups. [c] Intramolecular hydrogen bond between hydroxylic and nitrogen of the aromatic ring. [d] Dihedral angle H-C_1-C_2-H provided by MMX program. [e] Calculated ^3J by the Altona equation.[13]

In order to calculate the conformational populations, the most stable rotamer of each type (A, B and C) have been selected taking into account the results of the energy minimization (Table 1). These rotamers are A_3, B_1 and C_2, with or without intramolecular association, except for compound **3c** in CD_3CN as solvent. In this case, the selected rotamers are A_3, B_1 and C_1 (the latter stabilized by the hydrogen bond OH/O_2S). Since the O-H/N intramolecular bonding is not established in rotamer C_2 for the sulfone **3c,** (Table 3), the conformational predominance of A_3, B_1 and C_1 may be justified after the following considerations: **(a)** the appropriate nitrogen atom of the pyrazine ring has a lower negative charge than that on the nitrogen atom of the isoquinoline or quinoline rings (sulfones **3a**, **3b**); **(b)** the pyrazine moiety of the C rotamers adopts the spatial arrangement represented in Figure 4 (I). This is the most stable conformer by rotation around the C_{Ar}-C_1 bond. However, intramolecular hydrogen bonding with the nitrogen atom of the heterocyclic ring (O-H/N) is only possible when the aromatic moiety adopts a suitable spatial arrangement (Figure 4, II), at the expense of a significant energy increase. This energy increase is not balanced by the formation of intramolecular hydrogen bonding in the rotamer C_2 of compound **3c**. On the other hand, the O-H/N intramolecular hydrogen bonding is prevented in CD_3CN, but the $O\text{-}H/O_2S$ association can be formed in this compound. Therefore, the predominant C-type conformer in CD_3CN is C_1 (stabilized by the hydrogen bond $O\text{-}H/O_2S$). When such intramolecular association is removed (in DMSO-d_6), rotamer C_2 is more stable than C_1.



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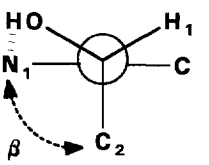

II

Rotamer	C_1	C_1 [a]	C_2	C_3	C_3 [a]
α (°)	57	59.6	64.4	48	48.2

Rotamer	C_2 [b]
β (°)	105

[a] Intramolecular hydrogen bond between hydroxyl and sulfonyl groups.
[b] Intramolecular hydrogen bond with the heterocyclic nitrogen atom.

Fig. 4. Rotamers around the C_{Ar}-C_1 bond in the type C conformers for sulfones **3a-c**.

For the hydroxy sulfone **3b**, the geometrical optimization indicates that the most stable rotamer by rotation around C_{Ar}-C_1 bond is II. Furthermore, the nitrogen atom of its isoquinoline ring is σ-rich (Figure 3).

These facts indicate that the O-H/N association is preferred in this compound (Table 3); therefore, rotamer C_2, with or without intramolecular association, is the predominant C-type one for this sulfone. Due to the low solubility of compound **3a**, its ^{1}H-NMR spectra was recorded only in DMSO-d_6 as solvent. In this case, the rotamer C_2 must be considered.

The conformational populations of all the investigated compounds were estimated from Equations (2) and (3) using the calculated $^3J_{ij}$ values for the selected rotamers and the experimentally observed vicinal coupling constants ($^3J_{ij}^{obs}$). The results have been collected in Table 1. The population of type A conformers (X_A) is higher than the participation of B- and C-type rotamers for all the sulfones studied herein. The X_A values are large but relatively smaller than those found for similar compounds.[2] The differences can be attributed to steric factors (due to the isoquinoline and quinoline rings) and the calculation methods. For the hydroxy sulfone **3b**, the X_A value increases when the solvent changes from DMSO-d_6 to $CDCl_3$. This fact is attributed to the intramolecular hydrogen association OH/N (Table 3), present in the conformation A_3 when the solvent is $CDCl_3$. This association contributes to the stabilization of A_3 in agreement to the considerations mentioned above. The variation of X_A with the solvent is not observed in the sulfone **3c**, since the conformation A_3 lacks of stabilization by intramolecular hydrogen bonding OH/N (Table 3).

The conformational behavior of methoxy sulfones **4a-b** is identical to the corresponding hydroxy sulfone **3a-c** in DMSO-d_6 (Table 1), a solvent in which intramolecular hydrogen bonding is inoperative. Thus, the most significant rotamers are identical to those discussed above, and the conformational populations are very similar as well.

The conformational distribution in methoxy sulfones supports the validity of the method used to carry out their conformational analysis. Application of the molecular mechanics force field MMX has made it possible to perform a suitable analysis of the conformational equilibria of β-hydroxy and β-methoxy sulfones with an heterocyclic ring at the β-position from the sulfur atom. Therefore, the results reported in this paper allow us to conclude that electrostatic interactions are the primary factors that control the conformational stability, due to the strong σ-deficient and σ-rich character of the sulfur atom and sulfonyl oxygen respectively. This fact leads to *almost* monoconformational hydroxy and methoxy sulfones. The role of intramolecular hydrogen bonding in such compounds is practically negligible.

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer 781 spectrophotometer. ^{1}H-NMR spectra were obtained at 25°C on a Varian T-60A (60 MHz) or a Varian VXR-300S (300 Mhz) spectrometer and the ^{13}C-

NMR spectra were recorded on a Varian FT-80A (20 MHz) or a Varian VXR-300S (75 MHz) spectrometer. Samples were prepared as solutions in $CDCl_3$, CD_3OD, CD_3CN, and DMSO-d_6 in 5 mm-o.d. tubes. Chemical shifts are reported in ppm downfield from tetramethylsilane (used as internal reference). The coupling constants are given in Hz.

Solvents were purified by the usual procedures.[16] Dimethyl sulfoxide (DMSO) was dried over calcium hydride and distilled under vacuum. Methyllithium was purchased from Aldrich, Janssen, or Merck. Silica gel used in column chromatography was Merck K-60 (230-400 mesh ASTM).

The geometrical optimization was performed using PCMODEL,[6] using the program default parameters (dielectric constant 1.5).

2-Ethoxycarbonylpyrazine (1c). This compound was prepared according to the procedure described elsewhere[3].

Oxo Sulfones. The synthesis of compounds **2a** and **2b** have been previously reported.[4]

2-(Methylsulfonyl)-1-(2-pyrazinyl)ethanone (2c). Sodium hydride (0.16 g, 6.58 mmol), dimethyl sulfone (0.62 g, 6.58 mmol) and 3.5 mL of dimethyl sulfoxide had been heated at 65°C with stirring under nitrogen for 30 min. The mixture was cooled and diluted with 5 mL of anhydrous tetrahydrofuran and then a solution of 2-ethoxycarbonylpyrazine (0.5 g, 3.29 mmol) in anhydrous THF (3 mL) was added slowly by syringe. The resulting mixture was heated to 65°C with stirring for 1 h and then cooled, hydrolyzed with water and extracted with chloroform. The aqueous phase was acidified to pH 7-8 by addition of concentrated hydrochloric acid and extracted with ether. After the organic phase had been dried with anhydrous magnesium sulfate, filtered, and evaporated. The β-oxo sulfone was recrystallized from ethyl acetate-hexane as an orange solid (0.36 g, 30%): IR (KBr), cm^{-1} : 3090, 3000, 2980, 1680, 1570, 1525, 1470, 1420, 1350, 1310, 1130, 840, 770; Anal. Calcd. for $C_7H_8N_2O_3S$: C, 41.99; H, 4.03; N, 13.99; O, 23.97; S, 16.01. Found: C, 42.03; H, 4.06; N, 13.95; O, 23.95; S, 16.01; ^1H NMR ($CDCl_3$), δ : 3.2 (s, 3H, CH_3), 5.0 (s, 2H, CH_2), 8.5-9.5 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$), δ : 42.10 (CH_3), 59.00 (CH_2), 143.63 (C-6), 144.25 (C-5), 145.96 (C-2), 148.75 (C-3), 189.92 (CO).

Hydroxy sulfones. General Procedure. 2-(Methylsulfonyl)-1-(2-quinolyl)ethanol (3a). Sodium borohydride (0.068 g, 1.79 mmol) was slowly added to a solution of **2a** (0.56 g , 2.24 mmol) in methanol. The mixture was stirred at room temperature for 1 h, followed by the addition of water. The solvent was removed and the residue extracted several times with chloroform. The organic phase was dried with anhydrous magnesium sulfate, filtered and evaporated to afford 0.514 g (91%) of **3a.** The solid was recrystallized from ethyl acetate-hexane to afford 0.32 g (57%) of crystalline white solid; mp 122-123°C. IR (KBr), cm^{-1} : 3260, 3000, 2900, 1590, 1560, 1500, 1450, 1430, 1310, 1285, 1125, 1075, 960, 835, 760; Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.36; H, 5.22; N, 5.58; O, 19.11; S, 12.73. Found : C, 57.38; H, 5.22; N, 5.55; O, 19.13;

S, 12.72; ^{1}H NMR (DMSO-d_6), δ : 3.14 (s, 3H, CH_3), 3.58 (ddd, 1H, J = 1.5, 2.7, 14.7 Hz, CH_2), 3.74 (dd, 1H, J = 9.9, 14.7 Hz, CH_2), 5.29 (ddd, 1H, J = 2.7, 5.4, 9.9 Hz, CH), 6.43 (d, 1H, J = 5.4 Hz, OH), 7.62-8.43 (m, 6H, Ar); ^{13}C NMR (DMSO-d_6), δ : 42.73 (CH_3), 59.98 (CH_2), 69.46 (CH), 118.70 (C-3), 126.42 (C-6), 127.07 (C-5), 127.78 (C-10), 128.50 (C-7), 129.73 (C-8), 136.99 (C-4), 146.42 (C-9), 161.86 (C-2).

2-(Methylsulfonyl)-1-(1-isoquinolyl)ethanol (3b). Prepared similarly, starting from compound **2b** and using ethanol as solvent. Recrystallized yield from ethyl acetate-hexane was 56%; mp 133-135°C. IR (KBr), cm^{-1} : 3200, 3100, 2900, 1615, 1580, 1555, 1490, 1445, 1320, 1300, 1120, 1085, 960, 810, 740; Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.36; H, 5.22; N, 5.58; O, 19.11; S, 12.73. Found : C, 57.39; H, 5.23; N, 5.55; O, 19.11; S, 12.72; ^{1}H NMR ($CDCl_3$), δ : 3.25 (d, 3H, J = 1.5 Hz, CH_3), 3.28 (dd, 1H, J = 9.9, 15.0 Hz, CH_2), 3.41 (ddq, 1H, J = 1.5, 1.8, 15.0 Hz, CH_2), 5.00 (bs, 1H, OH), 6.04 (dd, 1H, J = 1.8, 9.9 Hz, CH), 7.69-8.46 (m, 6H, Ar); ^{1}H NMR (DMSO-d_6), δ : 3.15 (s, 3H, CH_3), 3.66 (ddd, 1H, J = 0.9, 3.0, 15.0 Hz, CH_2), 3.96 (dd, 1H, J = 9.0, 15.0 Hz, CH_2), 5.88 (bs, 1H, OH), 6.29 (bd, 1H, J = 9.0 Hz, CH), 7.71-8.49 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$), δ: 42.90 (CH_3), 63.10 (CH_2), 65.47 (CH), 121.76 (C-4), 123.44 (C-5), 124.17 (C-9), 127.81 (C-7), 128.52 (C-8), 131.00 (C-6), 136.68 (C-10), 140.20 (C-3), 156.68 (C-1); ^{13}C NMR (DMSO-d_6), δ: 42.53 (CH_3), 59.45 (CH_2), 66.59 (CH), 120.97 (C-4), 125.05 (C-5), 125.41 (C-9), 127.27 (C-7), 127.54 (C-8), 130.26 (C-6), 136.13 (C-10), 140.73 (C-3), 158.82 (C-1)

2-(Methylsulfonyl)-1-(2-pyrazinyl)ethanol (3c). Treatment of compound **2c** (0.16 g, 0.8 mmol), sodium borohydride (0.021 g, 0.56 mmol) and methanol (7 mL) by the same procedure as used in the synthesis of compounds **3a** and **3b**, gave title product **3c** (0.11 g, 69%). The solid was recrystallized from chloroform-hexane to yield **3c** as a white solid (48%); mp 100-102°C; IR (KBr), cm^{-1}: 3200, 3010, 3000, 2900, 1520, 1470, 1410, 1325, 1290, 1120, 1070, 970, 845, 750; Anal. Calcd. for $C_7H_{10}N_2O_3S$: C, 41.58; H, 4.99; N, 13.86; O, 23.75; S, 15.82. Found : C, 41.60; H, 5.00; N, 13.84; O, 23.74; S, 15.82; ^{1}H NMR (CD_3CN), δ : 3.04 (bs, 3H, CH_3), 3.46 (ddq, 1H, J = 1.2, 3.0, 15.0 Hz, CH_2), 3.57 (dd, 1H, J = 9.3, 15.0 Hz, CH_2), 4.37 (bs, 1H, OH), 5.32 (dd, 1H, J = 3.0, 9.3 Hz, CH), 8.20-9.20 (m, 3H, Ar); ^{1}H NMR (DMSO-d_6), δ : 3.10 (s, 3H, CH_3), 3.47 (ddd, 1H, J = 1.2, 2.7, 14.7 Hz, CH_2), 3.70 (dd, 1H, J = 9.3, 14.7 Hz, CH_2), 5.20 (bd, 1H, J = 9.3 Hz, CH), 6.41 (bs, 1H, OH), 8.49-8.82 (m, 3H, Ar); ^{13}C NMR (CD_3OD), δ : 43.46 (CH_3), 61.02 (CH_2), 69.28 (CH), 143.78 (C-5), 144.87, 144.89 (C-3 and C-6), 145.05 (C-2); ^{13}C NMR (DMSO-d_6), δ : 42.72 (CH_3), 59.39 (CH_2), 67.52 (CH), 142.83 (C-5), 143.47, 143.77 (C-3 and C-6), 156.46 (C-2).

Methoxy sulfones. General Procedure. 2-(Methylsulfonyl)-1-(methoxy)-1-(2-quinolyl)ethane (4a). Methyllithium (1.20 mL of 1.6 M solution, 1.87 mmol) was added slowly with stirring under nitrogen to 1.2 mL of dimethyl sulfoxide at 20-22°C. The mixture was stirred for 45 min. Then, a solution of 0.47 g (1.87 mmol) of **3a** in 2.0 mL of anhydrous dimethyl sulfoxide and 0.2 mL (2.06 mmol) of dimethyl sulfate were

added by syringe. The mixture was stirred for 10 min at 20-22°C. The reaction mixture was hydrolyzed with water and extracted with chloroform. The organic extracts were washed with water, dried over magnesium sulfate and evaporated. The DMSO was removed by vacuum distillation (0.1 mmHg, 60°C). The residue was recrystallized from ethyl acetate-hexane to yield 0.18 g of **4a** (38%); mp 103-105°C; IR (KBr), cm^{-1} : 3080, 2950, 2845, 1590, 1560, 1500, 1475, 1445, 1320, 1280 1150, 1125, 960, 840 770; Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; O, 18.10; S, 12.06. Found : C, 58.90; H, 5.67; N, 5.27; O, 18.12; S, 12.03; ^1H NMR ($CDCl_3$), δ : 3.12 (d, 3H, J = 1.2 Hz, CH_3SO_2), 3.39 (ddq, 1H, J = 1.2, 2.4, 15.3 Hz, CH_2), 3.44 (s, 3H, OCH_3), 3.66 (dd, 1H, J = 10.2, 15.3 Hz, CH_2), 5.10 (dd, 1H, J = 2.4, 10.2 Hz, CH), 7.54-8.25 (m, 6H, Ar); ^1H NMR (DMSO-d_6), δ : 3.13 (s, 3H, CH_3SO_2), 3.33 (s, 3H, OCH_3), 3.55 (dd, 1H, J = 2.5, 15.0 Hz, CH_2), 3.98 (dd, 1H, J = 10.0, 15.0 Hz, CH_2), 5.04 (dd, 1H, J = 2.5, 10.0 Hz, CH), 7.69-8.66 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$), δ: 43.32 (CH_3SO_2), 57.40 (OCH_3), 60.01 (CH_2), 79.77 (CH), 118.20 (C-3), 126.88 (C-6), 127.52 (C-5), 127.64 (C-10), 129.07 (C-7), 129.95 (C-8), 137.46 (C-4), 147.71 (C-9), 157.98 (C-2); ^{13}C NMR (DMSO-d_6), δ : 42.77 (CH_3SO_2), 57.13 (OCH_3), 58.24 (CH_2), 78.72 (CH), 119.12 (C-3), 127.06 (C-6), 127.40 (C-5), 127.56 (C-10), 128.14 (C-7), 130.91 (C-8), 139.39 (C-4), 144.98 (C-9), 158.30 (C-2).

2-(Methylsulfonyl)-1-(methoxy)-1-(1-isoquinolyl)ethane (4b). Prepared by the same procedure used for compound **4a**, the product obtained was chromatographed on flash silica gel column, eluting successively with ethyl acetate-hexane (70:30), ethyl acetate and ethyl acetate-methanol (70:30) to yield **4b** (64%) as an orange oil which solidified upon treatment with hexane; recrystallized from ethanol-hexane as a crystalline white solid (27%); mp 110-112°C; IR (KBr), cm^{-1} : 3090, 2930, 2840, 1610, 1580, 1550, 1480, 1445, 1325, 1290, 1150, 1120, 960, 810, 750; Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; O, 18.10; S, 12.06. Found : C, 58.82; H, 5.70; N, 5.27; O, 18.12; S, 12.08; ^1H NMR (DMSO-d_6), δ : 3.15 (s, 3H, CH_3SO_2), 3.21 (s, 3H, OCH_3), 3.70 (dd, 1H, J = 3.3, 15.0 Hz, CH_2), 4.18 (dd, 1H, J = 9.0, 15.0 Hz, CH_2), 5.60 (dd, 1H, J = 3.3, 9.0 Hz, CH), 7.75-8.55 (m, 6H, Ar); ^{13}C NMR (DMSO-d_6), δ : 42.48 (CH_3SO_2), 55.93 (OCH_3), 57.21 (CH_2), 77.14 (CH), 121.57 (C-4), 124.80 (C-5), 126.13 (C-9), 127.66 (C-7), 128.03 (C-8), 130.60 (C-6), 136.64 (C-10), 141.44 (C-3), 156.37 (C-1).

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