Synthesis, Configurational Assignment, and Conformational Analysis of β-Hydroxy Sulfoxides, Bioisosteres of Oxisuran Metabolites, and Their *O*-Methyl Derivatives

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Received February 8, 1994 (Revised Manuscript Received June 9, 1994®)

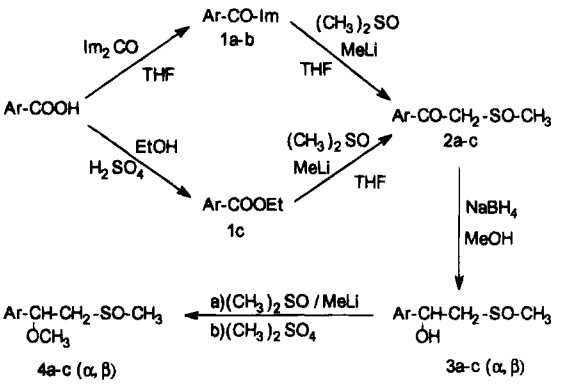
Synthesis, configurational assignment, and conformational analysis of diastereoisomers of 2-(methylsulfinyl)-1-(2-quinolyl)ethanol, **3a**, 2-(methylsulfinyl)-1-(1-isoquinolyl)ethanol, **3b**, 2-(methylsulfinyl)-1-(2-pyrazyl)ethanol, **3c**, and their *O*-methyl derivatives **4a–c** are reported. The configurational assignment and conformational analysis of the two diastereoisomers of β-hydroxy sulfoxides and β-methoxy sulfoxides have been carried out from the observed vicinal coupling constants using the molecular mechanics force field (MMX) and the Altona relationship as fundamental tools. The confomational equilibrium is explained in terms of polar and steric factors. Of significant importance was the role of intramolecular hydrogen bonding in the *RS*/*SR* isomers of β-hydroxy sulfoxides.

Oxisuran (2-(methylsulfinyl)-1-(1-pyridyl)ethanone) and its metabolites are immunosuppressive agents which have been reported to have the unique property of inhibiting cell-mediated immunity without any concomitant suppression of humoral antibody formation.[1] These compounds have prompted the study of several series of bioisosteres incorporating different heterocyclic systems.[2] In many cases, they are less toxic than oxisuran and may be used as potential immunosuppressants. Despite the interest in these drugs, little is understood of their action mechanism or their drug–receptor interactions. Conformational analysis and configurational assignment of oxisuran and its bioisosteres and metabolites are the first stage in order to clarify the relationships between the structure of these compounds (conformational behavior) and their associated pharmacological properties.

A correct analysis of conformational equilibria can be carried out using the molecular mechanics force field MMX[3] (derived from the MMP2 program),[4] as we have previously reported.[5] The validity of this method was tested studying monoconformational compounds.[5]

In the present paper, we report the synthesis, configurational assignment, and conformational analysis of several bioisosteres of oxisuran and its metabolites, in which the pyridine moiety has been replaced by quinoline, isoquinoline, and pyrazine rings (see Scheme 1).

Scheme 1



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

Results and Discussion

Synthesis. The synthetic pathways used in the preparation of compounds **1–4a–c** are shown in Scheme 1. β-Oxo sulfoxides **2a** and **2b** were prepared following a method previously reported.[6] The synthesis of **2c** by the same procedure was unsuccessful probably due to the low solubility of pyrazinic acid in THF. This low solubility prevents the formation of the imidazolide. Compound **2c** was synthesized by acylation of lithium (methylsulfinyl)methylide with 2-(ethoxycarbonyl)pyrazine.

The reduction of the carbonyl group of compounds **2a–c** with $NaBH_4$ yielded β-hydroxy sulfoxides **3a–c** as a mixture of two diastereoisomers (designated as α and β according to their NMR spectroscopic patterns) without any observable asymmetric induction. The separation of both epimeric compounds was achieved by column chromatography on silica gel.

The mixture of the epimeric hydroxy sulfoxides was methylated by reaction with dimethyl sulfate in the

® Abstract published in *Advance ACS Abstracts*, September 1, 1994.

(1) (a) Freedman, H. A.; Fox, A. E.; Shavel, J.; Morrison, G. C. *Proc. Soc. Exp. Biol. Med.* **1972**, *139*, 909. (b) Husberg, B.; Penn, I. *Ibid.* **1974**, *145*, 669. (c) Briziarelli, G.; Abruptyn, D.; Tornaben, J. A.; Schwartz, E. *Toxicol. Appl. Pharmacol.* **1976**, *36*, 49. (d) Kazmer, J. S.; Daddona, P. E.; Dalke, A. P.; Kelly, W. N. *Biochem. Pharmacol.* **1983**, *32*, 805.

(2) (a) García-Ruano, J. L.; Pedregal, C.; Rodríguez, J. H. *Tetrahedron* **1987**, *43*, 4407. (b) Alcudia, F.; Fernández, I.; Trujillo, M.; Zorrilla, F.; Marhuenda, E. *Mag. Reson. Chem.* **1988**, *26*, 687. (c) Alcudia, F.; Fernández, I.; LLera, F. M.; Trujillo, M.; Zorrilla, F. *Tetrahedron* **1989**, *45*, 1491.

(3) Software package PCMODEL, "Molecular Modeling for Personal Computers and Workstations", Serena Software, Bloomington, IN, versión 4.0 (1992).

(4) Allinger, N. L.; Flanagan, H. L. *J. Comput. Chem.* **1983**, *4*, 399.

(5) Alvarez-Ibarra, C.; Cuervo, R.; Fernández-Monreal, M. C.; Ruiz, M. P. *J. Org. Chem.* **1992**, *57*, 4270.

(6) Alvarez-Ibarra, C.; Cuervo-Rodríguez, R.; Fernández-Monreal, M. C.; García, F. J.; Martin, J. *J. Org. Chem.* **1989**, *54*, 5620.

0022-3263/94/1959-7284$04.50/0

Table 1. ^{1}H-NMR Parameters and Conformational Populations of Isomers α and β of Compounds -3a-c

		δ (ppm)					J (Hz)				conformer, %[a]			rotamers[b]		
compd	solvent	H_1	H_2	H_3	OH	CH_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{1,OH}$	X_A	X_B	X_C	A	B	C
3aα	$CDCl_3$	5.51	3.29	3.12	5.55	2.74	2.6	10.5	−12.9	–	87	1	12	A_1	B_3	C_1[c]
	DMSO-d_6	5.18	3.19	3.16	6.26	2.63	2.8	11.0	−12.9	5.1	92	4	4	A_1	B_3	C_2
3aβ	$CDCl_3$	5.54	3.46	3.16	5.69	2.77	3.0	8.1	−13.5	–	62	8	30	A_2'[c]	B_2'	C_3'[c]
	DMSO-d_6	5.27	3.24	3.43	6.16	2.72	7.4	5.1	−13.2	5.4	19	53	28	A_1'	B_2'	C_2'
3bα	$CDCl_3$	6.04	3.28	2.94	5.20	2.70	1.5	10.5	−12.9	–	95	0	5	A_1[d]	B_3[d]	C_1[c]
	DMSO-d_6	5.76	3.15	3.48	6.15	2.65	2.7	10.5	−12.9	6.6	88	7	5	A_1	B_3	C_1
3bβ	$CDCl_3$	6.20	3.43	2.98	5.62	2.89	2.7	8.1	−14.1	–	64	0	36	A_2'[c]	B_2'[d]	C_2'[d]
	DMSO-d_6	5.74	3.50	3.22	5.94	2.62	6.0	6.3	−12.9	6.6	35	38	27	A_1'	B_2'	C_1'
3cα	$CDCl_3$	5.49	3.26	3.18	5.63	2.73	2.6	9.6	−13.2	5.4	77	2	21	A_1	B_3	C_1[c]
	DMSO-d_6	5.09	3.10	3.14	6.28	2.62	2.7	10.8	−12.9	5.7	90	5	5	A_1	B_3	C_2
3cβ	$CDCl_3$	5.52	3.41	3.12	5.21	2.77	2.7	9.0	−13.2	3.9	73	6	21	A_2'[c]	B_2'	C_3'[c]
	DMSO-d_6	5.17	3.18	3.34	6.18	2.68	6.9	5.4	−13.2	5.7	22	47	31	A_1'	B_2'	C_2'

[a] Calculated conformational populations. [b] Selected rotamers for calculation of the conformational populations. [c] Intramolecular hydrogen bonding with the sulfinyl group. [d] Intramolecular hydrogen bonding with the nitrogen of the aromatic ring.

Table 2. ^{1}H-NMR Parameters and Conformational Populations of Isomers α and β of Compounds 4a-c

		δ (ppm)					J (Hz)			conformer, %[a]			rotamers[b]		
compd	solvent	H_1	H_2	H_3	OCH_3	CH_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	X_A	X_B	X_C	A	B	C
4aα	$CDCl_3$	5.02	3.20	3.23	3.43	2.67	2.4	10.2	−13.5	87	9	4	A_1	B_3	C_2
	DMSO-d_6	4.83	3.05	3.35	3.29	2.61	2.1	10.4	−13.2	90	6	4	A_1	B_3	C_2
4aβ	$CDCl_3$[c]	5.00	–	–	3.40	2.74	–	–	–	–	–	–	–	–	–
	DMSO-d_6[c]	4.90	–	–	3.28	2.68	–	–	–	–	–	–	–	–	–
4bα	$CDCl_3$	5.71	3.12	3.49	3.40	2.67	2.4	10.1	−13.2	88	10	2	A_1	B_3	C_1
	DMSO-d_6	5.43	3.09	3.65	3.22	2.63	2.5	10.1	−13.5	88	12	0	A_1	B_3	C_1
4bβ	$CDCl_3$	5.75	3.45	3.42	3.39	2.77	6.0	6.9	−13.5	38	39	22	A_1'	B_2'	C_1'
	DMSO-d_6	5.54	3.54	3.48	3.24	2.70	6.5	6.6	−13.2	34	45	21	A_1'	B_2'	C_1'
4cα	$CDCl_3$	4.91	3.09	3.21	3.45	2.67	2.5	10.3	−13.2	88	11	1	A_1	B_3	C_2
	DMSO-d_6	4.79	3.07	3.29	3.31	2.64	2.4	10.4	−13.2	90	9	1	A_1	B_3	C_2
4cβ	$CDCl_3$	4.95	3.26	3.29	3.44	2.74	7.0	5.3	−13.4	22	46	32	A_1'	B_2'	C_2'
	DMSO-d_6	4.87	3.34	3.37	3.33	2.70	7.0	5.6	−13.5	25	47	28	A_1'	B_2'	C_2'

[a] Calculated conformational populations. [b] Selected rotamers for calculation of the conformational populations. [c] Deceptively simple spectrum.

presence of (methylsulfinyl) methylide as base, to afford the epimeric methoxy sulfoxides **4a-c**, which were separated by column chromatography on silica gel.

Configurational Assignment and Conformational Analysis. The ^{1}H-NMR parameters of compounds **3a-c** and **4a-c**, which are relevant for this conformational analysis, are collected in Tables 1 and 2. The remaining parameters can be found in the Experimental Section.

The spectra were recorded in $CDCl_3$ and DMSO-d_6 to obtain information about the influence of solvent polarity on the conformational equilibria. As can be seen from the data of Table 1, the experimental values of the vicinal coupling constants, $J_{1,2}$ and $J_{1,3}$ in $CDCl_3$, are markedly varied, for all compounds. On change of solvent to DMSO-d_6, the experimental coupling constants, $J_{1,2}$ and $J_{1,3}$, are markedly varied for only the α-epimers (**3a**α, **3b**α, and **3c**α) but these constants for the β-epimers (**3a**β, **3b**β, and **3c**β) show no (or only a slight) variation.

On the other hand, the compound **3c**β displays, in $CDCl_3$, a low vicinal $J_{1,OH}$ coupling constant (3.9 Hz; Table 1). This value is in good agreement with a spatial arrangement in which there is an intramolecular OH-OS association.[7] The value of this coupling in DMSO-d_6 increases to 5.7 Hz (Table 1) indicating the destruction of that association. The epimer **3c**α displays in $CDCl_3$ and DMSO-d_6 vicinal $J_{1,OH}$ values (5.4 and 5.7 Hz, respectively) which are incompatible with the intramolecular association above mentioned. This vicinal coupling $J_{1,OH}$ constant was only observed in DMSO-d_6, with values between 5.1 and 6.6 Hz, for the other compounds (see Table 1).

These facts indicate that the preferred conformer in the β-epimers of the hydroxy sulfoxides **3a-c** in $CDCl_3$ is stabilized by an intramolecular hydrogen bond. When this intramolecular association is suppressed by the solvent (DMSO-d_6) the conformational equilibria are drastically changed to other more stable conformers and the $J_{1,2}$ and $J_{1,3}$ values become very similar. On the contrary, the solvent effect on the conformational equilibria of α-epimers is negligible. Therefore, the most significant conformer should not be stabilized by intramolecular hydrogen bonding.

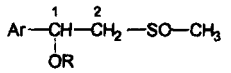
The *O*-methyl derivatives **4a-c** exhibit in $CDCl_3$ and DMSO-d_6 vicinal $J_{1,2}$ and $J_{1,3}$ constants (Table 2) which are very similar to those observed for the hydroxy sulfoxides **3a-c** in DMSO-d_6 (Table 1). This experimental fact supports the hypothesis indicated above.

The configurational assignment and conformational analysis of the diastereoisomers α and β of compounds **3a-c** and **4a-c** have been carried out from the experimentally observed vicinal coupling constants ($J_{1,2}$ and $J_{1,3}$), using the molecular mechanics force field (MMX)[3] as the fundamental tool.

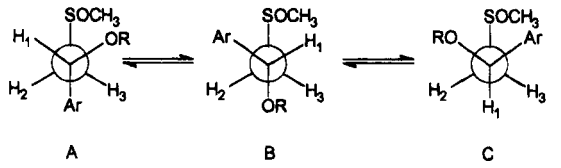
The staggered conformations around the CH-CH_2 bond for both diastereoisomers are shown in Figure 1. Rotation around the CH_2-S bond gives rise to three rotamers for each conformer of Figure 1. These new additional conformers are designated with the subscripts 1, 2, and 3 and they are collected in Figures 2 and 3.

Hydroxy Sulfoxides. In the α epimers, a marked difference between the two vicinal coupling $J_{1,2}$ and $J_{1,3}$ constants has been observed (Table 1). This fact indi-

(7) (a) Abraham, R. J.; Bakke, J. M. *Tetrahedron* **1978**, *34*, 2947. (b) Jochims, J. C.; Taigel, G.; Seeliger, A.; Lutz, P.; Driesen, H. E. *Tetrahedron Lett.* **1967**, 4363. (c) Moniz, W. B.; Poranski, C. F., Jr.; Hall, T. N. *J. Am. Chem. Soc.* **1966**, *88*, 190.



3a-c, 4a-c



A B C

Figure 1. Staggered conformations resulting from the rotation of the C_1–C_2 bond.

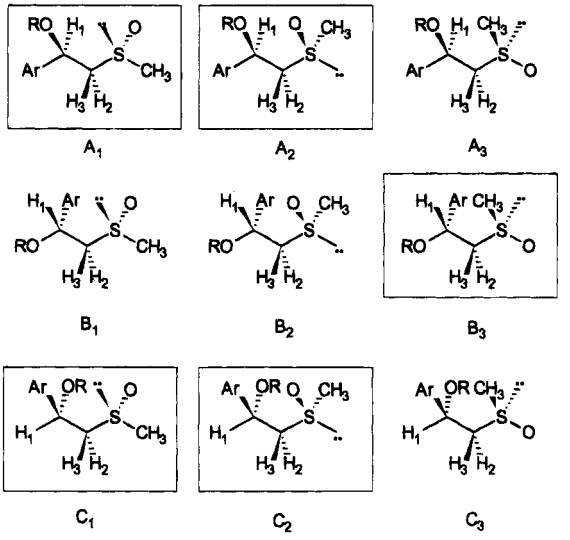


Figure 2. Staggered rotamers around the C_1–C_2 and C_2–S bonds for diastereoisomer *RR/SS*.

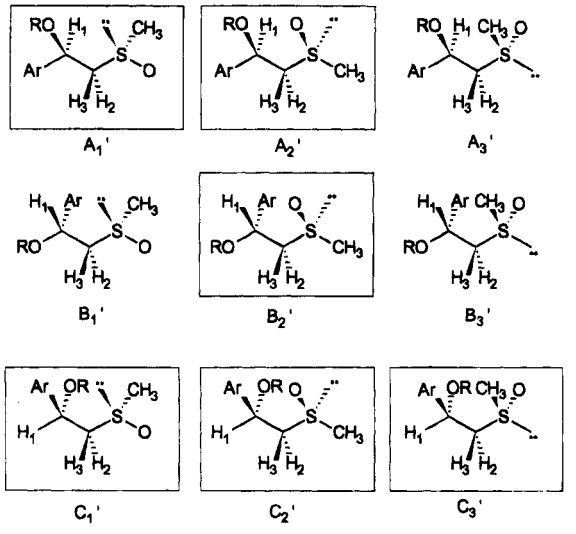


Figure 3. Staggered rotamers around the C_1–C_2 and C_2–S bonds for diastereoisomer *RS/SR*.

cates a clear predominance of either conformer A or conformer B in the conformational equilibria, because in conformer C, $J_{1,2}$ and $J_{1,3}$ values would be similar (Figure 1).

A marked preference for either conformer A or conformer B is also observed in $CDCl_3$ for β-epimers (very different $J_{1,2}$ and $J_{1,3}$ values), and this conformational preference decreases in DMSO-d_6 ($J_{1,2}$ and $J_{1,3}$ values are very close).

Considering the nine possible conformations for each diastereoisomer (Figures 2 and 3), the most significant of each type is chosen as a function of steric and polar criterions before submitting them to a geometry optimization by energy minimization using the molecular mechanics force field (MMX).[3] Thus, the selected conformers (pointed out with a box) do not bear 1,3-parallel interactions between second row atoms of the Periodic Table, except when intramolecular hydrogen bonding is possible. Nevertheless, calculations using the MMX program for the C_2, C_1', and C_2' rotamers were also performed in order to check the validity of this criterion.

In the hydroxy sulfoxides there are two intramolecular hydrogen bonding possibilities: the OH–sulfur function and the OH–N (of the aromatic ring) associations. The intramolecular association with the nitrogen of the heterocycle ring was considered in the process of the geometry optimization when the hydrogen bond with the sulfur function was impossible. The association with the nitrogen of the heterocycle ring is possible in all rotamers, when the aromatic ring is isoquinoline (**3b**α and **3b**β). However, when the aromatic ring is quinoline or pyrazine (**3a**α, **3a**β, **3c**α, and **3c**β), the intramolecular hydrogen bond with the nitrogen is only possible for rotamers C_1' and C_2'. This intramolecular association is only possible when the aromatic ring adopts a suitable spatial arrangement by rotation around the C_{Ar}–C_1 bond.

The proportion of conformers of type A (Figure 1) have to be higher than the participation of rotamers of type B for all compounds in $CDCl_3$ from the following considerations: (a) The size of an heteroaromatic ring is larger than that of any oxygenated function[8] and therefore, the steric interactions of the $SOCH_3$ group will bring about the relative stability sequence A > B > C; (b) the intramolecular hydrogen bonding between the OH and the oxygen of the sulfoxide group will stabilize the rotamers A and C with respect to rotamers B; (c) the electrostatic attraction between the negatively charged oxygen of the hydroxylic group and the electron-deficient sulfur atom of the sulfinyl group will again contribute to an increase of stability of rotamers A and C *vs* rotamers B. In addition the rotamers of type B have a destabilizing polar interaction between the σ-deficient sulfur of the sulfinyl group and the closest aromatic carbon.

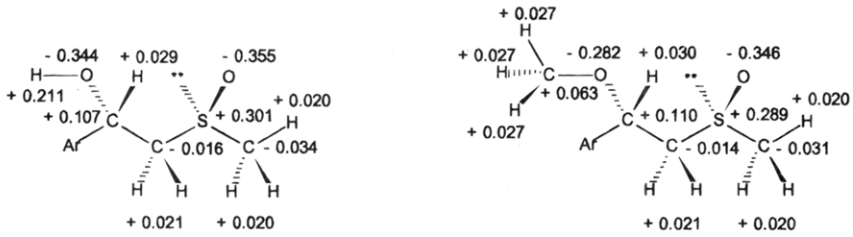
The energy of these polar interactions can be estimated as −2.3 kcal/mol for OH/SO groups and +0.5 kcal/mol for C_{Ar}/SO groups taking into account the model proposed by Zefirov,[9] the residual charges for the involved atoms calculated from the Rescha program[10] (Figure 4), the distances between groups deduced from the geometrical optimization with the MMX program[3] and eq 1 proposed by Abraham.[11] e_X and e_Y being residual charges for

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

groups X and Y (expressed as a fraction of the elemental electric charge) and $r_{X/Y}$ the distance (Å) between groups X and Y.

Assuming the predominance of conformers of type A, and taking into account the experimentally observed

(8) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.
(9) Zefirov, N. S.; Gurvich, L. G.; Shashkow, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211.
(10) (a) Baumer, L.; Sala, G.; Sello, G. *Tetrahedron Comput. Methodol.* **1989**, *2*, 37. (b) Baumer, L.; Sala, G.; Sello, G. *Ibid.* **1989**, *2*, 93. (c) Baumer, L.; Sala, G.; Sello, G. *Ibid.* **1989**, *2*, 105.
(11) Abraham, R. J.; Rossetti, Z. L. *J. Chem. Soc., Perkin Trans. 2* **1973**, 582.



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

Compound	3a	3b	3c	4a	4b	4c
C_{Ar}	+0.067	+0.067	+0.068	+0.065	+0.065	+0.068
N	-0.201	-0.202	-0.149[a] -0.153[b]	-0.195	-0.196	-0.147[a] -0.151[b]

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

Figure 4. Residual charges (fraction of elemental electric charge) of the atoms for compounds **3a−c** and **4a−c**.

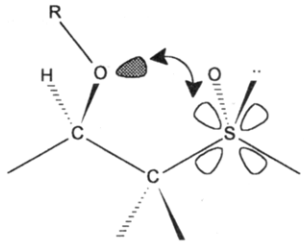


Figure 5. Donor--acceptor n−d^0 interaction in A_1 rotamer.

values for vicinal $J_{1,2}$ and $J_{1,3}$ coupling constants (Table 1), α-sulfoxides have to exhibit a more marked participation of rotamers A than the corresponding β epimers. The observed behavior is opposite for both diastereoisomers when the solvent is changed from $CDCl_3$ to DMSO-d_6.Thus, the preference for rotamers A increases for α epimers while it decreases for β epimers. On the other hand, an unequivocal assignment of H_2 and H_3 signals from the coupling constants data (Table 1; Figure 1) can be established from the predominance of rotamers of type A.

The most populated rotamers of type A in the *RR/SS* diastereoisomer (Figure 2) have to be the A_1 and A_2 conformations (the last stabilized by hydrogen bonding). The rotamer A_1 should be more stable than A_2 because the $(O/H)_{1,3\text{-p}}$ interaction seems to be stabilizing[12] whereas a $(Me/H)_{1,3\text{-p}}$ interaction must be slightly destabilizing.[13] On the other hand, the apparent electrostatic repulsion between the sulfur and oxygen lone electron pairs is negligible for the rotamer A_1. The undirectional character of the sulfur lone pair in similar sulfoxides has been clearly established by Day et al.[14] Furthermore, the geometry of the rotamer A_1 is suitable for the development of a stabilizing donor−acceptor interaction between an unshared electron pair of the oxygen of the hydroxyl group and a properly oriented empty *d* orbital of sulfur[2a] (Figure 5). CNDO/2 studies for similar sulfoxides have shown that the unassociated rotamer A_1 is more stable than the rotamer A_2.[15]

However the rotamer A_2' is much more stable than the conformer A_1' for the *RS/SR* diastereoisomer (Figure 3). The energy minimization derived from the molecular mechanics MMX force field[3] indicates that the relative energy differences of the conformer A_2' (stabilized by an intramolecular hydrogen bond) with the rotamer A_1' are 1.3, 2.7, and 3.1 kcal/mol when the heterocyclic ring is isoquinoline, quinoline, and pyrazine, respectively.

Taking into account the $(H/Me)_{1,3\text{-p}}$ and the $(O/H)_{1,3\text{-p}}$ interactions computed for rotamers of type B, the conformer B_2' for the *RS/SR* diastereoisomer has to be more stable than the rotamer B_3 for the *RR/SS* diastereoisomer. A relative energy differences between these two rotamers of 1.3, 1.7, and 1.5 kcal/mol have been calculated from energy minimization (obtained from the geometrical optimization with the MMX program[3]) when the heterocyclic ring is isoquinoline, quinoline, and pyrazine, respectively. Thus, the conformational populations for B_2' in the *RS/SR* isomers have to be higher than the participation of B_3 in *RR/SS* isomers. This fact should be most marked in DMSO-d_6, when the stabilizing hydrogen bond is absent. In this solvent, the rotamer B_2' should be more stable than the conformer A_1'.

On these assumptions, the *RS/SR* configuration can be assigned to the β isomers because a high participation of rotamers of type B is consistent with the proposed configurational assignment. The low participation of rotamers B for α isomers is in agreement with the *RR/SS* configuration.

Analysis of Vicinal Coupling Constants. Equations 2 and 3 have been widely applied in conformational analysis.[15]

$$^3J_{ij}^{\text{obs}} = \sum x_n {}^3J_{ij} \tag{2}$$

$$\sum x_n = 1 \tag{3}$$

The application of these equations to the experimentally observed $^1H-^1H$ vicinal coupling constants for the $CH-CH_2$ rotational system (Table 2) involves a previous evaluation of the theoretical coupling constants of rotamers A, B, and C (Figure 1). This evaluation has been carried out by means of the empirical equation of Karplus type proposed by Altona et al.[16] (eq 4) for an ethane fragment with three substituents ($CH-CH_2$). This em-

(12) Allinger, N. L.; Hirfch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1969**, *91*, 337.
(13) Frieze, D. M.; Evans, S. A. *J. Org. Chem.* **1975**, *40*, 2690.
(14) Day, R. O.; Kingsbury, C. A.; Day, V. W. *J. Org. Chem.* **1981**, *46*, 1004.

(15) (a) Alcudia, F.; Carreño, M. C.; García-Ruano, J. L.; Rodríguez, J. H.; Secundino, M. A. *An. Quim.* **1982**, *78C*, 374. (b) Brunet, E.; García-Ruano, J. L.; Rodríguez, J. H.; Secundino, M. A.; García de la Vega, J. M. *J. Mol. Struct.* **1986**, *144*, 109. (c) Brunet, E.; García-Ruano, J. L.; Hoyos, M. A.; Rodríguez, J. H.; Prados, P.; Alcudia, F. *Org. Mag. Reson.* **1983**, *21*, 643.
(16) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

Table 3. Dihedral Angles and Calculated $^3J_{ij}$ of the Considerate Rotamers for the Diastereomer *RR/SS* of the Compounds 3a–c

		rotamers[a]								
compd		A_1	A_1[b]	A_2[c]	B_3	B_3[b]	C_1	C_1[c]	C_2	C_3
3a	H_1–H_2[d]	302.10	–	291.70	173.97	–	57.54	62.43	58.52	–
	H_1–H_3[d]	185.20	–	175.19	57.51	–	301.09	305.26	303.83	–
	$J_{1,2}$[e]	2.41	–	1.42	11.20	–	4.23	3.53	4.09	–
	$J_{1,3}$[e]	11.66	–	11.24	4.48	–	2.05	2.54	2.37	–
3b	H_1–H_2[d]	297.60	289.79	290.87	173.39	177.02	53.91	53.67	66.67	–
	H_1–H_3[d]	179.00	172.13	173.46	56.9	60.54	297.99	297.43	312.18	–
	$J_{1,2}$[e]	1.92	1.29	1.36	11.16	11.39	4.78	4.82	2.97	–
	$J_{1,3}$[e]	11.47	10.99	11.11	4.58	4.03	1.73	1.68	3.48	–
3c	H_1–H_2[d]	299.70	–	291.94	176.34	–	57.14	62.26	59.89	56.60
	H_1–H_3[d]	183.05	–	175.45	59.79	–	300.63	305.10	305.01	301.07
	$J_{1,2}$[e]	2.14	–	1.43	11.35	–	4.29	3.56	3.89	4.37
	$J_{1,3}$[e]	11.62	–	11.26	4.14	–	2.00	2.52	2.51	2.05

[a] Rotamers submitted to energy minimization. [b] Intramolecular hydrogen bond between OH and N of the aromatic ring. [c] Intramolecular hydrogen bond between hydroxylic and sulfinyl groups. [d] Dihedral angle H–C_1–C_2–H provided by MMX program. [e] Calculated ^3J by the Altona equation.[16]

Table 4. Dihedral Angles and Calculated $^3J_{ij}$ of the Considerate Rotamers for the Diastereomer *RS/SR* of the Compounds 3a–c

		rotamers[a]									
compd		A_1'	A_1'[b]	A_2'[c]	B_2'	B_2'[b]	C_1'	C_1'[b]	C_2'	C_2'[b]	C_3'[c]
3a	H_1–H_2[d]	293.51	–	293.14	172.11	–	62.19	57.91	56.62	58.95	58.78
	H_1–H_3[d]	176.70	–	175.43	54.77	–	306.59	302.78	299.76	303.17	303.47
	$J_{1,2}$[e]	1.55	–	1.52	11.06	–	3.57	4.18	4.37	4.03	4.05
	$J_{1,3}$[e]	11.34	–	11.26	4.90	–	2.71	2.24	1.20	2.29	2.32
3b	H_1–H_2[d]	292.74	293.59	296.79	172.85	172.09	55.20	54.35	49.09	57.67	48.59
	H_1–H_3[d]	176.08	177.13	179.66	55.41	54.78	299.79	298.75	294.86	301.04	294.27
	$J_{1,2}$[e]	1.49	1.56	1.84	11.12	11.06	4.58	4.71	5.52	4.22	5.59
	$J_{1,3}$[e]	11.30	11.37	11.50	4.80	4.90	1.91	1.81	1.46	2.05	1.41
3c	H_1–H_2[d]	295.90	–	293.62	172.42	–	–	54.62	57.44	60.89	56.77
	H_1–H_3[d]	179.38	–	175.88	55.22	–	–	239.11	300.50	304.01	301.19
	$J_{1,2}$[e]	1.76	–	1.56	11.09	–	–	4.67	4.25	3.75	4.35
	$J_{1,3}$[e]	11.49	–	11.29	4.83	–	–	5.26	1.99	2.39	2.06

[a] Rotamers submitted to energy minimization. [b] Intramolecular hydrogen bond between OH and N of the aromatic ring. [c] Intramolecular hydrogen bond between hydroxylic and sulfinyl groups. [d] Dihedral angle H–C_1–C_2–H provided by MMX program. [e] Calculated ^3J by the Altona equation.[16]

pirical equation relates the ^1H–^1H vicinal coupling constants with the values of dihedral angles, the electronegativity of the substituents attached to the rotational system, and their relative orientation with respect to the considered protons.[17]

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

Calculations of the theoretical vicinal coupling constants ($^3J_{ij}$) for all considered rotamers (Figures 2 and 3) were carried out from eq 4 using the electronegativity of the atoms directly linked to the CH–CH_2 rotational system proposed by Huggins[18] and the dihedral angles provided by the geometrical optimization established with the MMX force field.[3] The results have been summarized in Tables 3 and 4.

The most stable rotamer of each type (A, B, and C; see Table 1) was selected taking into account the results of the energy minimization obtained with the MMX force field.[3] Then, the conformational populations of all compounds were estimated from eqs 2 and 3 using the calculated values for $^3J_{ij}$ of the selected rotamers and the experimentally observed vicinal coupling constants ($^3J_{ij}^{obs}$). The results have been collected in Table 1.

The different conformational behavior observed in the studied compounds can be justified from the most stable rotamers selected by the MMX force field.

α-Epimers. The rotamer A_1 is much more stable than B_3, C_1, or C_2. As a consequence, the population of conformers of type A is higher than the participation of rotamers of type B and C, in $CDCl_3$ and DMSO-d_6, for all compounds. The rotamers A_1, B_3, and C_1 (the latter stabilized by hydrogen bonding) in $CDCl_3$ and A_1, B_3, and C_2 in DMSO-d_6 have been considered for α epimers of compounds **3a**α and **3c**α. The most stable rotamer of type C is the conformer C_2, when the previously mentioned intramolecular association is destroyed in DMSO-d_6. Thus, the population of the rotamers of type A (X_A) increases at the expense of the population of the rotamers C (X_C) when the solvent changes from $CDCl_3$ to DMSO-d_6.

In concordance with the conformational behavior observed, the rotamers A_1, B_3, and C_1, with or without hydrogen bonding, have been considered as significant conformations in $CDCl_3$ and DMSO-d_6, respectively, for the α epimer of the compound **3b**.

The population of the rotamers C (X_C) values and their variations with the solvent are small in all cases studied. However, some differences between the compound **3b**α and other α epimers have been observed. In DMSO-d_6,

(17) (a) Jackman, L. M.; Sternhell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1978. (b) Kagan, H. B. *Determination of Configurations by Spectrometric Methods*; Georg Thiense: Stuttgart, 1977, Vol. 1, pp 63–75. (c) Forrest, T. P.; Sukumar, S. *Can. J. Chem.* **1977**, *55*, 3686. (d) Wasylishen, R. E.; Chun, K.; Bukata, J. *Org. Magn. Reson.* **1977**, *9*, 473. (e) Bhaua, N. S.; Williams, D. H. *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964.

(18) Huggins, M. L. *J. Am. Chem. Soc.* **1953**, *75*, 4123.

Table 5. Dihedral Angles and Calculated $^3J_{ij}$ of the Considerate Rotamers for Compounds 4a–c

diastereomer		rotamers[a]									
		RR/SS					*RS/SR*				
compd		A_1	B_3	C_1	C_2	C_3	A_1'	B_2'	C_1'	C_2'	C_3'
4a	H_1-H_2[b]	291.79	174.97	59.99	59.21	57.72	297.82	174.13	57.75	55.93	61.32
	H_1-H_3[b]	173.72	58.83	303.62	304.79	302.19	181.26	56.81	302.39	299.31	307.16
	$J_{1,2}$[c]	1.42	11.27	3.88	3.99	4.21	1.94	11.21	4.20	4.47	3.69
	$J_{1,3}$[c]	11.13	4.28	2.34	2.48	2.17	11.57	4.59	2.20	1.86	2.78
4b	H_1-H_2[b]	289.91	176.33	47.34	65.40	53.37	298.93	173.04	60.67	55.86	–
	H_1-H_3[b]	171.58	59.90	293.48	311.22	298.29	182.51	55.68	305.61	299.52	–
	$J_{1,2}$[c]	1.30	11.35	5.78	3.13	4.86	2.05	11.14	3.78	4.48	–
	$J_{1,3}$[c]	10.94	4.12	1.35	3.34	1.76	11.61	4.76	2.58	1.89	–
4c	H_1-H_2[b]	292.10	177.46	66.44	61.10	56.29	298.55	173.55	58.36	56.62	61.08
	H_1-H_3[b]	173.99	61.14	310.53	306.55	300.74	181.99	56.28	302.98	299.93	306.81
	$J_{1,2}$[c]	1.44	11.41	3.00	3.72	4.42	2.01	11.17	4.11	4.37	3.72
	$J_{1,3}$[c]	11.15	3.94	3.24	2.70	2.01	11.59	4.67	2.26	1.93	2.74

[a] Rotamers submitted to energy minimization. [b] Dihedral angle $H-C_1-C_2-H$ provided by MMX program. [c] Calculated ^3J by the Altona equation.[16]

when the intramolecular association by hydrogen bonding is prevented, the most stable rotamer of type C is C_2 for compounds **3a**α and **3c**α because the conformer C_1 (without hydrogen bonding) presents a strong destabilizing interaction $(O/OH)_{1,3\text{-p}}$. However, the rotamer C_1 for compound **3b**α is more stable than C_2, because in the former the isoquinoline ring adopts a spatial arrangement which locates the nitrogen at an adequate distance from the σ-deficient sulfur atom (3.14 Å) to develop a polar stabilizing interaction. Furthermore, the isoquinoline ring places the nitrogen near to the σ-rich sulfinyl oxygen (3.04 Å) in rotamer C_2, and a destabilizing polar interaction is operative.

β-Epimers. The population of the rotamers A (X_A) is the highest in $CDCl_3$ because the rotamer A_2' (stabilized by the hydrogen bond OH/OS) is the most stable. However, a different conformational behavior between **3b**β and the other β epimers of compounds **3a** and **3c** has been observed. Thus, the most significant conformer of type C in $CDCl_3$ is C_3' (stabilized by the hydrogen bond OH/OS) for compounds **3a**β and **3c**β, and C_2' (stabilized by intramolecular association between hydroxyl group and the aromatic nitrogen) for **3b**β. The isoquinoline ring in the rotamer C_3', places the nitrogen close to the methyl carbon, and a polar destabilizing interaction is present together with a strong destabilizing steric interaction $(Ar/Me)_{1,3\text{-p}}$.

The conformational equilibria change drastically in DMSO-d_6. The rotamer B_2' is more stable than the conformation A_1' for all compounds. The population of rotamers of type B increases at the expense of the population of rotamers of type A, and the population of rotamers of type C is also important (Table 1).

In this sense, the most stable conformer of type C is obviously C_2' for compounds **3a**β and **3c**β. However, this conformer is 1.2 kcal/mol less stable than C_1' for compound **3b**β. This change can be reasonably interpreted as the isoquinoline ring adopts a spatial arrangement which places the nitrogen at an adequate distance from the σ-deficient sulfur atom (3.27 Å) to develop a polar stabilizing interaction in the rotamer C_1'. Furthermore, the isoquinoline ring locates the nitrogen near to the sulfinyl oxygen (3.35 Å) in the rotamer C_2' and as consequence a destabilizing polar interaction is operative.

Methoxy Sulfoxides. The dihedral angles, provided by the MMX program, together with the vicinal coupling constants calculated from by Altona equation[16] (eq 4) for all rotamers submitted to geometry optimization, have been collected in Table 5. The most stable rotamer of each type (A, B, and C) and the calculated conformational populations are shown in Table 2.

The conformational behavior of methoxy sulfoxides **4a–c** is identical to the corresponding hydroxy sulfoxides **3a–c** in DMSO-d_6 (see Tables 1 and 2), where intramolecular hydrogen bonding is inoperative. Thus the most significant rotamers are identical and the conformational populations are obviously very similar. As a consequence, the *RR/SS* configuration can be assigned to α epimers and the *RS/SR* configuration to β epimers.

The conformational behavior of methoxy sulfoxides supports the validity of the method used to achieve the configurational assignment and conformational analysis.

The application of molecular mechanics force field MMX has made it possible to perform a suitable analysis of conformational equilibria and the configurational assignment of β-hydroxy and β-methoxy sulfoxides with a heterocyclic ring at the β-position of the sulfur atom. The conformational equilibria are conditioned by polar and steric factors, and the role of the intramolecular hydrogen bond, especially in the β epimers of the hydroxy sulfoxides, is very important.

Experimental Section

Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H (300 MHz) and ^{13}C (75 MHz) spectra were recorded at 25 °C on a Varian VXR-300S spectrometer. Samples were prepared as solutions in $CDCl_3$ and DMSO-d_6 in 5 mm o.d. tubes. The chemical shifts are quoted as δ values from tetramethylsilane as internal reference.

Solvents were purified by the usual procedure.[19] Dimethyl sulfoxide (DMSO) was dried over calcium hydride and distilled under vacuum. Methyllithium was purchased from Aldrich Chemical Co., Janssen Chimica Beerse, and Merck A. G. Silica gel used in column chromatography was Merck K-60 (230–400 mesh ASTM).

The geometrical optimization was performed using PCMODEL,[3] with default parameters (dielectric constant 1.5).

2-(Ethoxycarbonyl)pyrazine (1c). A mixture of 1 g (8.06 mmol) of 2-pyrazinecarboxylic acid, 9 mL of absolute ethyl alcohol, and 1.5 mL of concentrated sulfuric acid was heated under reflux for 7 h. Then, the reaction mixture was poured over ice and made alkaline with ammonium hydroxide and extracted with chloroform. The organic extracts were dried with anhydrous magnesium sulfate, filtered, and evaporated. The residue was recrystallized from hexane to afford 0.9 g of

(19) Vogel, A. *Textbook of Practical Organic Chemistry*; Longman: New York, 1988.

yellow needles (74%): mp 50–51 °C; IR (KBr) cm^{-1} 3040, 3000, 2950–2850, 1740, 1570, 1470, 1440, 1420, 1370, 1310, 1155, 770, 720; ^1H NMR ($CDCl_3$) δ 1.48 (t, 3H, J = 7.2 Hz, CH_3), 4.53 (q, 2H, J = 7.2 Hz, CH_2), 8.75–9.33 (m, 3H, Ar); ^{13}C NMR δ 13.99 (CH_3), 62.11 (CH_2), 143.31 (C-2), 144.13 (C-3), 146.00 (C-6), 147.35 (C-5), 163.65 (CO).

Oxo Sulfoxides. The synthesis of compounds **2a** and **2b** have been previously described.[6]

2-(Methylsulfinyl)-1-(2-pyrazyl)ethanone (2c). Methyllithium (10.28 mL of 1.6 M solution, 16.45 mmol) was added slowly with stirring under nitrogen to a mixture of dimethyl sulfoxide (1.4 mL, 19.74 mmol) and THF (30 mL) at 0 °C. The mixture was allowed to reach room temperature and stirred for 40 min. Then, a solution of 2-(ethoxycarbonyl)pyrazine (1 g, 6.58 mmol) in anhydrous THF (5 mL), was added slowly by syringe, and the mixture was stirred for 3 h at room temperature. The reaction mixture was hydrolyzed with water (20 mL) and extracted with chloroform. The aqueous phase was acidified to pH 6–7 by addition of concentrated hydrochloric acid and extracted with chloroform, and the organic phase was dried with anhydrous magnesium sulfate, filtered, and evaporated. The unreacted DMSO was removed by vacuum distillation (0.1 mmHg, 60 °C), and the solid was recrystallized from ethyl acetate–hexane to yield 0.36 g (30%): mp 98–100 °C; IR (KBr) cm^{-1} 3040, 3000, 2980, 2890, 1685, 1570, 1525, 1470, 1400, 1350, 1010, 845, 770; ^1H NMR ($CDCl_3$) δ 2.81 (s, 3H, CH_3), 4.59–4.77 (AB system, 2H, δ_A = 4.68, δ_B = 4.62, J = 13.5 Hz, CH_2), 8.71–9.29 (m, 3H, Ar); ^{13}C NMR δ 48.34 (CH_3), 69.05 (CH_2), 152.44 (C-6), 152.59 (C-5), 155.19 (C-2), 157.38 (C-3), 201.54 (CO). Anal. Calcd for $C_7H_8N_2O_2S$: C, 45.64; H, 4.38; N, 15.21; O, 17.37; S, 17.40. Found: C, 45.20; H, 4.72; N, 15.32; O, 17.39; S, 17.35.

Hydroxy Sulfoxides. General Procedure. 2-(Methylsulfinyl)-1-(1-isoquinolyl)ethanol (3b). Sodium borohydride (0.023 g, 0.6 mmol) was slowly added to a solution of **2b** (0.2 g, 0.858 mmol) in 7 mL of 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 0.188 g (93%) of **3b** as a brown oil. A 48:52 mixture of the two diastereoisomeric sulfoxides was observed by ^1H-NMR and ^{13}C-NMR spectroscopy. The crude oil was chromatographed on a flash silica gel column, eluting successively with ethyl acetate–hexane (70:30; 90:10), ethyl acetate, and ethyl acetate–methanol (99:1–30:70) to yield the minor diastereoisomer **3b**α as a pure product. The other isomeric product **3b**β was isolated with 86% of purity: IR (film) cm^{-1} 3260, 3100, 2920, 1605, 1580, 1550, 1490, 1435, 1360, 1085, 1035, 810, 755. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.26; H, 5.57; N, 5.96; O, 13.61; S, 13.60. Found: C, 61.27; H, 5.55; N, 5.95; O, 13.63; S, 13.60.

Compound **3b**α: ^1H NMR ($CDCl_3$) δ 2.70 (s, 3H, CH_3), 2.94 (dd, 1H, J = 10.5, 12.9 Hz, CH_2), 3.28 (dd, 1H, J = 1.5, 12.9 Hz, CH_2), 5.20 (bs, 1H, OH), 6.04 (dd, 1H, J = 1.5, 10.5 Hz, CH), 7.66–8.47 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.65 (s, 3H, CH_3), 3.15 (dd, 1H, J = 2.7, 12.9 Hz, CH_2), 3.48 (dd, 1H, J = 10.5, 12.9 Hz, CH_2), 5.76 (ddd, 1H, J = 2.7, 6.6, 10.5 Hz, CH), 6.15 (d, 1H, J = 6.6 Hz, OH), 7.65–9.00 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.73 (CH_3), 64.36 (CH_2), 64.62 (CH), 121.45 (C-4), 123.92 (C-5), 124.49 (C-9), 127.63 (C-7), 128.22 (C-8), 130.81 (C-6), 136.61 (C-10), 140.39 (C-3), 157.97 (C-1).

Compound **3b**β: ^1H NMR ($CDCl_3$) δ 2.89 (s, 3H, CH_3), 2.98 (dd, 1H, J = 8.1, 14.1 Hz, CH_2), 3.43 (dd, 1H, J = 2.7, 14.1 Hz, CH_2), 5.62 (bs, 1H, OH), 6.20 (dd, 1H, J = 2.7, 8.1 Hz, CH), 7.64–8.46 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.62 (s, 3H, CH_3), 3.22 (dd, 1H, J = 6.3, 12.9 Hz, CH_2), 3.50 (dd, 1H, J = 6.0, 12.9 Hz, CH_2), 5.74 (ddd, 1H, J = 6.0, 6.3, 6.6 Hz, CH), 5.94 (d, 1H, J = 6.6 Hz, OH), 7.55–8.40 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 37.22 (CH_3), 58.02 (CH_2), 61.89 (CH), 120.36 (C-4), 123.04 (C-5), 123.55 (C-9), 126.49 (C-7), 127.07 (C-8), 129.65 (C-6), 135.57 (C-10), 139.25 (C-3), 157.31 (C-1).

2-(Methylsulfinyl)-1-(2-quinolyl)ethanol (3a). Standard workup yielded 74% of a mixture of the two diastereoisomers (44:56 ratio by NMR) of the hydroxy sulfoxide **3a**. The isomers were separated by flash chromatography on silica gel column eluting successively with ethyl acetate and ethyl acetate–methanol (95:5; 90:10). The minor diastereoisomer **3a**α was isolated as a pure orange oil. The β epimer could not be isolated in pure state. Spectroscopic data was obtained from enriched samples of **3a**β: IR (film) cm^{-1} 3280, 3060–2900, 1590, 1550, 1500, 1455, 1420, 1365, 1075, 1035, 1020, 780, 760. Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.26; H, 5.57; N, 5.96; O, 13.61; S, 13.60. Found: C, 61.29; H, 5.55; N, 5.94; O, 13.62; S, 13.62.

Compound **3a**α: ^1H NMR ($CDCl_3$) δ 2.74 (s, 3H, CH_3), 3.12 (dd, 1H, J = 10.5, 12.9 Hz, CH_2), 3.29 (dd, 1H, J = 2.6, 12.9 Hz, CH_2), 5.55 (bs, 1H, OH), 5.51 (dd, 1H, J = 2.6, 10.5 Hz, CH), 7.53–8.23 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.63 (s, 3H, CH_3), 3.12–3.19 (ABX system, 2H, δ_A = 3.19, δ_B = 3.16, J = 2.8, 11.0, 12.9 Hz, CH_2), 5.15–5.20 (ABX system, 1H, δ = 5.18, J = 5.1 Hz, CH), 6.26 (d, 1H, J = 5.1 Hz, OH), 7.58–8.57 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.28 (CH_3), 61.99 (CH_2), 67.98 (CH), 117.78 (C-3), 126.70 (C-6), 127.51 (C-5, C-10), 128.40 (C-7), 129.83 (C-8), 137.57 (C-4), 146.41 (C-9), 159.56 (C-2).

Compound **3a**β: ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H, CH_3), 3.16 (dd, 1H, J = 8.1, 13.5 Hz, CH_2), 3.46 (dd, 1H, J = 3.0, 13.5 Hz, CH_2), 5.54 (dd, 1H, J = 3.0, 8.1 Hz, CH), 5.69 (bs, 1H, OH), 7.51–8.20 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.72 (s, 3H, CH_3), 3.24 (dd, 1H, J = 7.4, 13.2 Hz, CH_2), 3.43 (dd, 1H, J = 5.1, 13.2 Hz, CH_2), 5.27 (ddd, 1H, J = 5.1, 5.4, 7.4 Hz, CH), 6.16 (d, 1H, J = 5.4 Hz, OH), 7.57–8.43 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.16 (CH_3), 59.58 (CH_2), 68.75 (CH), 117.99 (C-3), 126.60 (C-6), 127.58 (C-5, C-10), 128.59 (C-7), 129.85 (C-8), 137.38 (C-4), 146.55 (C-9), 159.75 (C-2).

2-(Methylsulfinyl)-1-(2-pyrazyl)ethanol (3c). Compound **3c** was obtained by standard workup (64%) as a mixture (44:56) of two diastereoisomers, which could not be isolated in pure form. Flash chromatography on silica gel column, eluting successively with ethyl acetate–hexane (70:30; 90:10), ethyl acetate, and ethyl acetate–methanol (99:1–30:70), yielded enriched samples of **3c**α and **3c**β from which their respective spectroscopic data was extracted: IR (film) cm^{-1} 3290, 3040, 3000, 2890, 1520, 1480, 1400, 1355, 1110, 1010, 950, 830, 750. Anal. Calcd for $C_7H_{10}N_2O_2S$: C, 45.15; H, 5.42; N, 15.05; O, 17.19; S, 17.19. Found: C, 45.17; H, 5.40; N, 15.02; O, 17.19; S, 17.22.

Compound **3c**α: ^1H NMR ($CDCl_3$) δ 2.73 (s, 3H, CH_3), 3.18 (dd, 1H, J = 9.6, 13.2 Hz, CH_2), 3.26 (dd, 1H, J = 2.6, 13.2 Hz, CH_2), 5.49 (ddd, 1H, J = 2.6, 5.4, 9.6 Hz, CH), 5.63 (d, 1H, J = 5.4 Hz, OH), 8.51–8.92 (m, 3H, Ar); ^1H NMR (DMSO-d_6) δ 2.62 (s, 3H, CH_3), 3.06–3.19 (ABX system, 2H, δ_A = 3.14, δ_B = 3.10, J = 2.7, 10.8, 12.9 Hz, CH_2), 5.06–5.12 (ABX system, 1H, δ = 5.09, J = 5.7 Hz, CH), 6.28 (d, 1H, J = 5.7 Hz, OH), 8.58–8.82 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 38.67 (CH_3), 60.00 (CH_2), 67.19 (CH), 143.23 (C-5), 143.50 (C-3), 144.00 (C-6), 156.23 (C-2).

Compound **3c**β: ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H, CH_3), 3.12 (dd, 1H, J = 9.0, 13.2 Hz, CH_2), 3.41 (dd, 1H, J = 2.7, 13.2 Hz, CH_2), 5.21 (d, 1H, J = 3.9 Hz, OH), 5.52 (ddd, 1H, J = 2.7, 3.9, 9.0 Hz, CH), 8.50–8.92 (m, 3H, Ar); ^1H NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 3.18 (dd, 1H, J = 6.9, 13.2 Hz, CH_2), 3.34 (dd, 1H, J = 5.4, 13.2 Hz, CH_2), 5.17 (ddd, 1H, J = 5.4, 5.7, 6.9 Hz, CH), 6.18 (d, 1H, J = 5.7 Hz, OH), 8.58–8.82 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 38.56 (CH_3), 58.54 (CH_2), 68.96 (CH), 143.10 (C-5), 143.46 (C-3), 144.06 (C-6), 156.12 (C-2).

Methoxy Sulfoxides. General Procedure. 2-(Methylsulfinyl)-1-methoxy-1-(1-isoquinolyl)ethane (4b). Methyllithium (1.64 mL of 1.6 M solution, 2.62 mmol) was added slowly with stirring under nitrogen to 1.6 mL of dimethyl sulfoxide at 20–22 °C. The mixture was stirred for 45 min. Then, a solution of 0.616 g (2.62 mmol) of **3b** in 2.5 mL of anhydrous dimethyl sulfoxide and 0.27 mL (2.88 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 purified by flash chromatography on silica gel column (ethyl acetate–methanol 70:30) to obtain 0.423 g (65%) of product

4b as an oil. A 55:45 mixture of the two diastereoisomeric sulfoxides was observed by ^1H and ^{13}C-NMR spectroscopy.

The oil was chromatographed on a flash silica gel column, eluting successively with ethyl acetate–hexane (70:30), ethyl acetate, and ethyl acetate–methanol (95:5–30:70) to yield the major diastereoisomer **4b**α as a pure product. The other isomeric product **4b**β was isolated with 85% purity: IR (film) cm^{-1} 3060, 2900, 2845, 1600, 1575, 1550, 1480, 1445, 1365, 1110, 1035, 960, 770 755. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62; O, 12.83; S, 12.86. Found: C, 62.62; H, 6.09; N, 5.59; O, 12.85; S, 12.85.

Compound **4b**α: ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H, CH_3), 3.12 (dd, 1H, J = 2.4, 13.2 Hz, CH_2), 3.40 (s, 3H, OCH_3), 3.49 (dd, 1H, J = 10.1, 13.2 Hz, CH_2), 5.71 (dd, 1H, J = 2.4, 10.1 Hz, CH), 7.63–8.58 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.63 (s, 3H, CH_3), 3.09 (dd, 1H, J = 2.5, 13.5 Hz, CH_2), 3.22 (s, 3H, OCH_3), 3.65 (dd, 1H, J = 10.1, 13.5 Hz, CH_2), 5.43 (dd, 1H, J = 2.5, 10.1 Hz, CH), 7.70–8.57 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.44 (CH_3), 57.04 (OCH_3), 60.74 (CH_2), 74.86 (CH), 121.07 (C-4), 123.44 (C-5), 126.31 (C-9), 127.51 (C-7), 127.72 (C-8), 130.21 (C-6), 136.46 (C-10), 141.89 (C-3), 156.85 (C-1).

Compound **4b**β: ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 3.38–3.50 (ABX system, 2H, δ_A = 3.45, δ_B = 3.42, J = 6.0, 6.9, 13.5 Hz, CH_2), 5.72-5.77 (ABX system, 1H, δ_X = 5.75, CH), 7.63–8.50 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.70 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.44–3.58 (ABX system, 2H, δ_A = 3.54, δ_B = 3.48, J = 6.5, 6.6, 13.2 Hz, CH_2), 5.52–5.56 (ABX system, 1H, δ = 5.54, CH), 7.71–8.57 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 38.68 (CH_3), 56.50 (OCH_3), 56.99 (CH_2), 74.99 (CH), 121.21 (C-4), 124.27 (C-5), 126.62 (C-9), 127.43 (C-7), 127.74 (C-8), 130.25 (C-6), 136.54 (C-10), 141.66 (C-3), 156.93 (C-1).

2-(Methylsulfinyl)-1-methoxy-1-(2-quinolyl)ethane (4a). Prepared by the same procedure used for compound **4b**, the product obtained was chromatographed on flash silica gel column (ethyl acetate–methanol 70:30) yielding **4a** (30%) as a 45:55 mixture of the two diastereoisomers. Pure **4a**α was obtained on a silica gel column eluting successively with ethyl acetate and ethyl acetate–methanol (90:10; 70:30). The β epimer could not be isolated pure. From the enriched mixtures of **4a**β we have extracted its spectroscopic data. IR (film) cm^{-1} 3090, 2950, 2840, 1595, 1550, 1500, 1475, 1440, 1365, 1100, 1030, 960, 820, 770. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62; O, 12.83; S, 12.86. Found: C, 62.65; H, 6.02; N, 5.61; O, 12.84; S, 12.88.

Compound **4a**α: ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H, CH_3), 3.15–3.28 (ABX system, 2H, δ_A = 3.23, δ_B = 3.20, J = 2.4, 10.2, 13.5 Hz, CH_2), 3.43 (s, 3H, OCH_3), 4.99–5.04 (ABX system, 1H, δ_X = 5.02, CH), 7.54–8.25 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.61 (s, 3H, CH_3), 3.05 (dd, 1H, J = 2.1, 13.2 Hz, CH_2), 3.29 (s, 3H, OCH_3), 3.35 (dd, 1H, J = 10.4, 13.2 Hz, CH_2), 4.83 (dd, 1H, J = 2.1, 10.4 Hz, CH), 7.58–8.48 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.78 (CH_3), 57.72 (OCH_3), 61.52 (CH_2), 78.70 (CH), 118.40 (C-3), 126.83 (C-6), 127.65 (C-5), 127.74 (C-10), 129.31 (C-7), 129.92 (C-8), 137.36 (C-4), 147.90 (C-9), 159.42 (C-2).

Compound **4a**β: ^1H NMR ($CDCl_3$) δ 2.74 (s, 3H, CH_3), 3.26–3.38 (ABX system, 2H, CH_2), 3.40 (s, 3H, OCH_3), 4.98–5.02 (ABX system, 1H, δ_X = 5.00, CH), 7.51–8.24 (m, 6H, Ar); ^1H NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 3.26–3.33 (ABX system, 2H, CH_2), 3.28 (s, 3H, OCH_3), 4.89–4.93 (ABX system, 1H, δ = 4.90, CH), 7.58–8.48 (m, 6H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.07 (CH_3), 57.39 (OCH_3), 59.27 (CH_2), 79.23 (CH), 118.52 (C-3), 126.85 (C-6), 127.69 (C-5), 128.70 (C-10), 129.17 (C-7), 129.93 (C-8), 137.44 (C-4), 147.73 (C-9), 159.40 (C-2).

2-(Methylsulfinyl)-1-methoxy-1-(2-pyrazyl)ethane (4c). Prepared similarly, starting from compound **3c**, the crude oil was purified by flash chromatography on a silica gel column (ethyl acetate–methanol 70:30) yielding 69% of the title compound **4c** as a mixture 46:54 (ratio by NMR) of two diastereoisomeric sulfoxides. The mixture was chromatographed on a flash silica gel column eluting successively with ethyl acetate–hexane (70:30), ethyl acetate, and ethyl acetate–methanol (95:5–70:30). The major diastereoisomer **4c**β was isolated as a pure product and the other isomeric product **4c**α with 90% purity: IR (film) cm^{-1} 3060, 3000, 2890, 2835, 1535, 1480, 1415, 1355, 1110, 1020, 960, 810, 755. Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.05; N, 14.00; O, 15.99; S, 15.98. Found: C, 50.01; H, 6.02; N, 14.03; O, 15.97; S, 15.98.

Compound **4c**α: ^1H NMR ($CDCl_3$) δ 2.67 (s, 3H, CH_3), 3.09 (dd, 1H, J = 2.5, 13.2 Hz, CH_2), 3.21 (dd, 1H, J = 10.3, 13.2 Hz, CH_2), 3.45 (s, 3H, OCH_3), 4.91 (dd, 1H, J = 2.5, 10.3 Hz, CH), 8.63–8.81 (m, 3H, Ar); ^1H NMR (DMSO-d_6) δ 2.64 (s, 3H, CH_3), 3.07 (dd, 1H, J = 2.4, 13.2 Hz, CH_2), 3.29 (dd, 1H, J = 10.4, 13.2 Hz, CH_2), 3.31 (s, 3H, OCH_3), 4.79 (dd, 1H, J = 2.4, 10.4 Hz, CH), 8.67–8.82 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 39.27 (CH_3), 57.54 (OCH_3), 60.64 (CH_2), 75.94 (CH), 142.84 (C-5), 144.19 (C-3 y C-6), 153.87 (C-2).

Compound **4c**β: ^1H NMR ($CDCl_3$) δ 2.74 (s, 3H, CH_3), 3.21–3.33 (ABX system, 2H, δ_A = 3.29, δ_B = 3.26, J = 5.3, 7.0, 13.4 Hz, CH_2), 3.44 (s, 3H, OCH_3), 4.93–4.977 (ABX system, 1H, δ_X = 4.95, CH), 8.55–8.80 (m, 3H, Ar); ^1H NMR (DMSO-d_6) δ 2.70 (s, 3H, CH_3), 3.31–3.40 (ABX system, 2H, δ_A = 3.37, δ_B = 3.34, J = 5.6, 7.0, 13.5 Hz, CH_2), 3.33 (s, 3H, OCH_3), 4.85–4.90 (ABX system, 1H, δ = 4.87, CH), 8.60–8.83 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$) δ 38.99 (CH_3), 57.22 (OCH_3), 57.75 (CH_2), 76.18 (CH), 143.19 (C-5), 144.24 (C-3), 144.28 (C-6), 153.98 (C-2).

Acknowledgment. R.C.R. greatfully acknowledges the Ministry of Education and Science for an F.P.I. grant. The NMR spectra have been registered with the NMR facilities supported by the Universidad Complutense de Madrid. This work has been supported by the "Comisión Asesora de Investigación Científica y Técnica" (CAICYT, No. PR-84-0352-C03-03), Ministerio de Educación y Ciencia (Madrid, Spain).