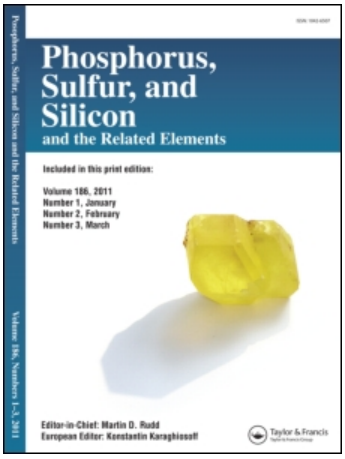

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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 2-METHYLTHIO DERIVATIVES OF 1-(2=THIENYL)ETHANOL AND THEIR OMETHYL DERIVATIVES

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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 2-METHYLTHIO DERIVATIVES OF 1-(2-THIENYL)ETHANOL AND THEIR *O*-METHYL DERIVATIVES

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The synthesis and conformational analysis of the title compounds are reported. The conformational properties of the 2-thienyl derivatives, deduced from ^{1}H-nmr and ir data, are compared with those for 2-furyl analogs and the results have been interpreted taking into account the stronger (OH...Ring) intramolecular association in the 2-furyl derivatives.

Key words: Conformational analysis; sulphur-oxygen interaction; hydrogen bonds; ^{1}H-nmr; ir.

INTRODUCTION

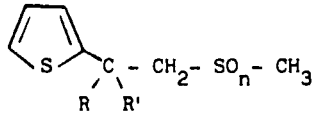
The pharmacological properties of many heteroaromatic compounds such as oxisuran and its metabolites,[1] which show immunosuppressive activity, have prompted us to study several series of analogous compounds with different heterocyclic systems. The interest of these derivatives resides in the fact that, in many cases, they are less toxic than oxisuran and may also be immunosuppressants. In this sense, we have recently communicated the preparation of some 2-methylthio derivatives of 1-(2-furyl)ethanol.[2] The immunosuppressive activity of some of these compounds was also evaluated.

In the present paper, we report on the synthesis and conformational analysis of a series of 2-methylthio derivatives of 1-(2-thienyl)ethanol and their *O*-methyl derivatives (Scheme 1). Taking into account the differences between the heteroaromatic rings, furane *versus* thiophene, it is worth studying the conformational preferences of this series of thioderivatives in order to evaluate the influence of the thienyl group upon the conformational stability. In addition, some modifications in the immunosuppressive activity can be expected, and pharmacological tests will be undertaken in later works. The toxicity of the (methylsulphinyl)methyl 2-thienyl ketone (**2**), bioisostere of oxisuran described in a previous paper,[1c] has already been tested and the results have shown that the thienyl derivative is less toxic than oxisuran.

RESULTS AND DISCUSSION

(a) Synthesis:

The preparation of (methylsulphonyl)methyl 2-thienyl ketone (**3**) was achieved by condensation of ethyl 2-thiophenecarboxylate with dimethylsulphone carbanion

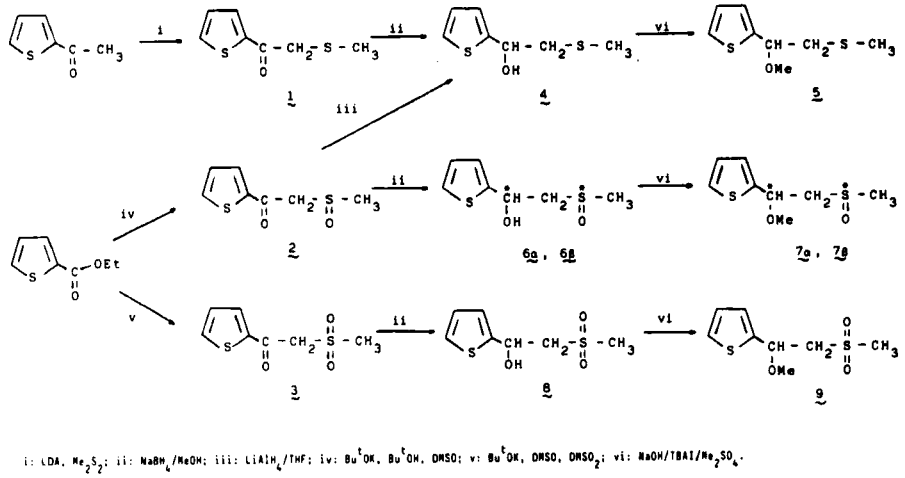


Compound	1	2	3	4	5	6α, 6β	7α, 7β	8	9
n	0	1	2	0	0	1	1	2	2
R	=O	=O	=O	H	H	H	H	H	H
R'				OH	OMe	OH	OMe	OH	OMe

SCHEME 1 List of studied compounds.

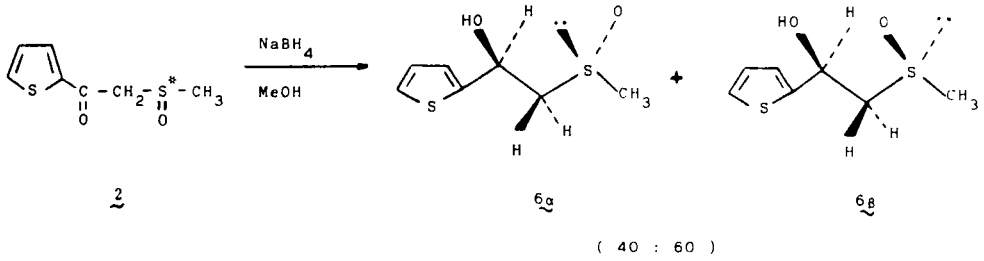
(see Scheme 2), and the reduction of **2** and **3** with sodium borohydride yielded the corresponding alcohols, 2-(methylsulphinyl)-1-(2-thienyl)ethanol (**6**) and 2-(methylsulphonyl)-1-(2-thienyl)ethanol (**8**), respectively. Compound **6** is a mixture of the two diastereomeric hydroxysulphoxides **6α** (*RS/SR*, 40%) and **6β** (*RR/SS*, 60%) (see Scheme 3), which was resolved by column chromatography. The configurational assignment was performed by ^{1}H-nmr and ^{13}C-nmr spectroscopy.[3,4] The asymmetric induction associated to the reduction of **2** with different metal hydrides has previously been investigated.[5]

The synthesis of 2-(methylsulphenyl)-1-(2-thienyl)ethanol (**4**) was carried out by two different methods. First, compound **2** was reduced with lithium aluminium hydride, but this procedure gave only a moderate yield of **4** (59% overall yield from ethyl 2-thiophenecarboxylate). In the second method, 2-acetylthiophene was treated with lithium diisopropylamine (LDA) to form the corresponding enolate,



i: LDA, Me_2S_2; ii: $NaBH_4$/MeOH; iii: $LiAlH_4$/THF; iv: Bu^tOK, Bu^tOH, DMSO; v: Bu^tOK, DMSO, $DMSO_2$; vi: NaOH/TBAI/Me_2SO_4.

SCHEME 2 Synthesis of compounds **1–9**.



2 6α 6β

SCHEME 3 Asymmetric reduction of (methylsulphinyl)methyl 2-thienyl ketone (**2**).

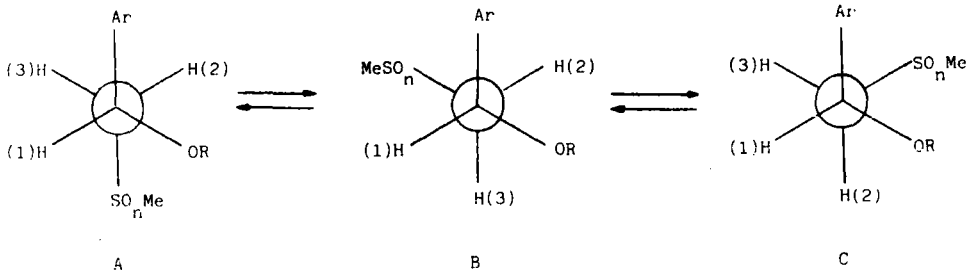
which was sulphenylated with dimethyldisulphide to give (methylsulphenyl)-methyl 2-thienyl ketone (**1**). Finally, the ketosulphide **1** was reduced with sodium borohydride to form **4** in 80% overall yield.

Methylation of compounds **4**, **6**α, **6**β, and **8**, under phase-transfer conditions[6] afforded the corresponding *O*-methyl derivatives: 1-methoxy-2-(methylsulphenyl)-1-(2-thienyl)ethane (**5**); (*RS*/*SR*)- and (*RR*/*SS*)-1-methoxy-2-(methylsulphinyl)-1-(2-thienyl)ethane (**7**α and **7**β); and 1-methoxy-2-(methylsulphonyl)-1-(2-thienyl)ethane (**9**), respectively.

(b) Conformational analysis

^{1}H-nmr spectra of all the substrates have been taken from $CDCl_3$ and DMSO-d_6 solutions in order to examine solvent effects. Because of the important role that intramolecular hydrogen bonding plays on the conformational stability of the hydroxy derivatives **4**, **6**α, **6**β, and **8**, some additional ^{1}H-nmr ($CDCl_3$) and ir ($CDCl_3$ and CCl_4) spectra have been recorded at different concentrations. It must be taken into account that in these compounds there are two intramolecular hydrogen bonding possibilities: the (O—H. . .Sulphur function) and the (O—H. . .Ring) associations. The frequencies for the absorptions of free O—H, which unfortunately overlap with those due to (O—H. . .Ring), and (O—H. . .Sulphur function), are listed in Table II. This overlapping is analogous to that described for 2-furfuryl and benzyl alcohols,[2,10] and also has been observed in our studies on 2-(hydroxymethyl)thiophene, which showed one only band at 3600 cm^{-1} at $c = 10^{-3}$ M in CCl_4. The parameters corresponding to the ABX patterns have been extracted from a computer-optimized analysis and are collected in Table I. These values ($J^{obs}_{i,j}$) correspond to a weighted mean (Equation 1), and the rotamer population can be determined provided that $J^{n}_{i,j}$ values for each conformation ($n = A$, B, and C. See Figure 1) are known. In this paper, they have been calculated according to Haasnoot *et al.*[7] (using Inamoto's electronegativities[8]) and by the method recently proposed by Colucci *et al.*[9] (values in brackets in Table I). As the results are quite similar, we will only refer to those obtained by the first method.

$$J^{obs}_{1,2(3)} = X_A J^{A}_{1,2(3)} + X_B J^{B}_{1,2(3)} + X_C J^{C}_{1,2(3)} \quad (1)$$



Ar= 2-Thienyl; R= H, Me; *n*= 0, 1, 2.

FIGURE 1 Rotamers *A*, *B* and *C* that arise from the rotation around the C—C bond for the 2-methylthio derivatives of 1-(2-thienyl)ethanol, **4–9**.

The hydroxythioether **4** exhibits a preference for the rotamer *A* in $CDCl_3$ (66%), that decreases when the solvent is changed (47% in DMSO-d_6) or the hydroxy group is protected ($x_A = 45$–48% for the *O*-methyl derivative **5**). This behaviour is different from that found for the analogous[2] 1-(2-furyl)-2-(methylsulphenyl)ethanol (**10**) whose conformational equilibrium is independent of the solvent and similar to that of its *O*-methyl derivative 1-(2-furyl)-1-methoxy-2-(methylsulphenyl)ethane (**11**), ($x_A \simeq 43\%$). Additionally, the value of $J_{(1,OH)}$ for **4** in $CDCl_3$ is lower than that found for the furyl derivative **10** (3.2 Hz and 4.9 Hz, respectively). When DMSO-d_6 is used as solvent, the value of this coupling constant increases significantly in compound **4**, $\Delta J_{(1,OH)} = +2$ Hz, meanwhile in **10** only increases +0.5 Hz. This behaviour is indicative of an important contribution of intramolecular association (O—H. . .S) in **4** which stabilizes the rotamer *A*, whereas the intramolecular hydrogen bonding with the thienyl ring seems to be less important than in the analogous furyl derivative **10**.[11] Data obtained from the ir studies are in concordance with the above exponded behaviour, showing a much higher fraction of intramolecular (O—H. . .S) associated molecules for **4** (65%) than for **10** (35%)[2] (Table II).

A similar behaviour was found for the hydroxysulphoxide **6**β[4]. Thus, the participation of rotamer *A* in $CDCl_3$ is higher for **6**β ($x_A^\beta \simeq 80\%$) than for its analogous (*RR/SS*)-1-(2-furyl)-2-(methylsulphinyl)ethanol, (**12**β) ($x_A^\beta \simeq 73\%$).[2] The $J_{(1,OH)}$ coupling constant increases in the opposite sense, 2.5 Hz in **6**β and 3.2 Hz in **12**β. Both data [x_A^β and $J_{(1,OH)}$] are indicative of a more important contribution of intramolecular association with the heterocycle ring in the furyl derivative **12**β than in **6**β (Figure 2). When hydrogen bonding is not operative (DMSO-d_6 as solvent or *O*-methyl compounds) the participation of rotamer *B* becomes as important as the contribution of rotamer *A*, being similar for both hydroxysulphoxides **6**β and **12**β, and their *O*-methyl derivatives ($x_A^\beta \simeq 43\%$). The favoured rotamers in β isomers when intramolecular association is destroyed, or does not exit are depicted in Figure 3.

With regard to α type diastereomers, instead of the previously invoked $n \Rightarrow d$

TABLE I

^{1}H-NMR parameters and conformational populations of compounds

Comp.	Solv.[b]	Conc. (w/v)	Chemical Shifts (ppm) H(1)	H(2)	H(3)	SO_nMe	OR	Coupling Constants (Hz) $J_{1,2}$	$J_{1,3}$	$-J_{2,3}$	$J_{1,OH}$
4	A[c]	3.0	5.04	2.86	2.95	2.13	3.09	8.7	4.0	13.8	3.2
	A[c]	1.5	5.04	2.87	2.96	2.12	3.06	8.7	4.0	13.8	3.2
	B	3.0	4.92	−2.76−		2.03	5.77	Deceptively simple spectrum			5.0
	C[d]	1.5	5.36	3.19	3.09	2.13	6.24	7.2	5.6	13.5	4.8
	D[d]	2.0	5.08	2.92	2.87	2.10	5.97	7.7	5.1	13.5	4.8
5	A	3.0	4.56	2.99	2.79	2.10	3.31	7.3	5.7	13.6	—
	B[e]	3.0	4.60	2.89	2.73	2.02	3.19	7.0	5.9	13.6	—
6α	A[c,f]	3.0	5.57	3.17	3.03	2.60	4.74	10.5	2.3	13.0	4.4
	A[c,f]	1.5	5.61	3.20	3.03	2.67	4.48	10.3	2.3	13.0	4.3
	A	0.5	5.67	3.24	3.00	2.70	4.07	10.0	2.3	13.2	4.1
	B	1.5	5.19	3.11	2.99	2.58	6.18	11.0	2.5	13.0	5.0
7α	A	3.0	4.99	3.15	3.01	2.63	3.37	11.2	2.4	13.0	—
	B	3.0	4.86	3.27	2.98	2.59	3.34	11.1	2.6	13.1	—
6β	A[e]	3.0	5.61	3.19	3.07	2.70	4.40	9.0	3.6	13.1	2.8
	A[g]	1.5	5.64	3.19	3.07	2.71	4.23	9.2	3.3	13.1	2.5
	A[h]	0.5	5.67	3.20	3.08	2.72	4.11	9.3	3.2	13.0	2.2
	A[h]	0.2	5.67	3.19	3.08	2.72	4.06	9.5	3.1	13.0	2.2
	B[e]	3.0	5.21	3.12	3.16	2.62	6.07	7.2	6.2	12.9	5.0
7β	A[e]	3.0	5.02	3.26	3.08	2.66	3.31	7.0	6.2	13.2	—
	B[e]	3.0	4.86	3.23	3.15	2.60	3.16	6.9	6.8	13.0	—
8	A[i,h]	3.0	5.60	3.56	3.28	3.04	3.20	10.3	1.7	14.8	3.2
	A[i,e]	1.0	5.62	3.57	3.30	3.04	3.09	10.2	1.9	14.6	3.4
	B[j,k]	3.0	5.29	3.63	3.33	3.02	6.32	9.9	2.9	14.6	5.2
9	A[e,k]	3.0	5.04	3.60	3.17	3.01	3.31	10.2	2.6	15.0	—
	B[e,k]	3.0	4.95	3.82	3.33	2.99	3.27	9.7	3.2	14.7	—

[a] Values in brackets have been obtained through Gandour's equation (see text).
[b] Solvents, A: $CDCl_3$, B: DMSO-d_6, C: DMSO-d_6-C_6D_6 (1:1), D: DMSO-d_6-C_6D_6 (3:1)
[c] $J_{(1,Ar)} = 0.6$ Hz. [d] $J_{(1,Ar)} = 0.7$ Hz. [e] $J_{(1,Ar)} = 0.5$ Hz. [f] $J_{(3,OH)} = 0.9$ Hz. [g] $J_{(1,Ar)} = 0.3$ Hz.
0.8 Hz, $J_{(2,Me)} = 0.5$ Hz, $J_{(3,Me)} = 0.8$ Hz. [j] $J_{(3,OH)} = 1.0$, $J_{(1,Ar)} = 0.8$ Hz. [k] $J_{(2,Me)} = 0.4$ Hz, $J_{($

TABLE II

IR O—H Stretching absorptions of compounds **4**, **6α**, **6β** and **8**. [ν_{OH} (cm^{-1})]

Comp.	Solv.[a]/ Conc. (M)	Free and (O—H...Ring) associated	(O—H...Sulphur function) intramolecular associated	$\Delta\nu$(cm^{-1})	%(O—H...O—S) associated molecules[b]
4	A/5 × 10^{-4}	3598	3500	98	65
6α	B/7 × 10^{-5}	3600	—	—	0
6β	B/5 × 10^{-4}	3590	3400	190	74
8	B/1 × 10^{-4}	3590	3548	42	35

[a] Solvents: A = CCl_4, B = $CDCl_3$.
[b] Estimated from the relative areas of both bands.

donor-acceptor interaction,[12] we have recently proposed an $n \Rightarrow \sigma^*_{S-R}$ stereoelectronic interaction, operative in conformer A_1^α (Figure 4), to explain the high participation of the rotamer *A* in all instances.[4] In $CDCl_3$, there is a slight decrease in the population of rotamer *A* for the furyl analogue (*RS*/*SR*)-1-(2-furyl)-2-(methylsulphinyl)ethanol (**12α**) (83%), compared with that for **6α** (87%). This difference is not evident when DMSO-d_6 is used as solvent or when the *O*-methyl derivatives are compared to each other. This behaviour has been attributed to the more important contribution of (O—H...Ring) intramolecular association in **12α**, which makes the stereoelectronic $n_O \Rightarrow \sigma^*_{S-R}$ interaction (responsible in great measure for the stability of A_1^α) more difficult, as compared with the situation in the thienyl derivative **6α** (Figure 4). When this (O—H...Ring) association is not operative (hydroxy derivatives in DMSO-d_6 and for *O*-methylated compounds) no differences are observed in x_A^β values (96–98%).

In the case of sulphones **8** and **9**, there is a high predominance of the rotamer *A* in all solvents (Table I). The appearance of the long-range coupling constants for the methylsulphonyl signals with H_2 and H_3 allowed us to analyse the relative stability of the different rotamers A_i (i = 1, 2, 3), that result from rotation around the CH_2—S bond[13] (Figure 5). The values of $^4J_{3,Me}$(0.8–1.0 Hz) are higher than those of $^4J_{2,Me}$(0.4–0.5 Hz), indicating that the rotamer A_3 predominates over A_2. Additionally, the high magnitude of $^3J_{(1,OH)}$(3.4 Hz) for **8** in $CDCl_3$ can only be explained by admitting an important participation of the rotamer A_3. These data are in agreement with the low proportion of (O—H...O—S—O) intramolecular

FIGURE 2 Competition between (O—H...O—S) and (O—H...Ring) intramolecular association for the hydroxysulphoxides **6β** and **12β**.

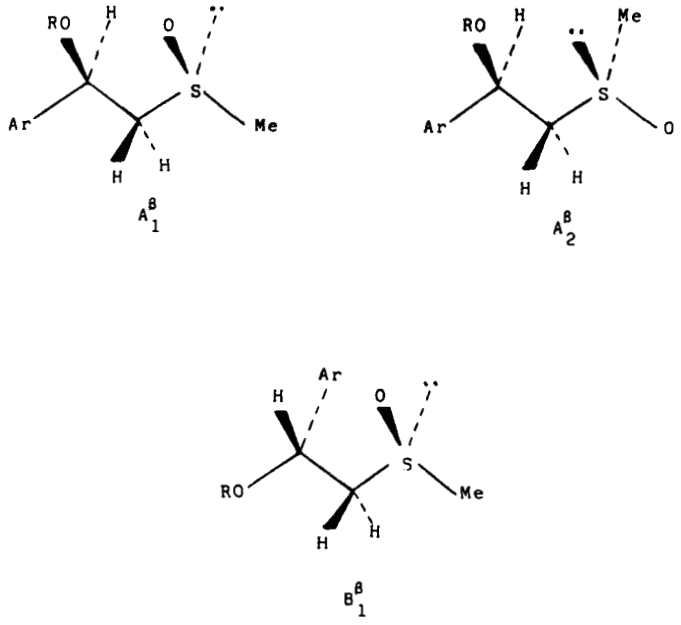


FIGURE 3 Favoured rotamers for sulphoxides **6**β in DMSO-d_6 and **7**β in all instances.

associated molecules deduced for **8** from its ir specra (≈35%, Table II). As in similar compounds,[14] these results may be attributed to an electrostatic attraction between the hydroxylic oxygen and the methyl group of the sulphone, which shares the positive charge of sulphur by delocalization,[15] stabilizing the rotamer A_3. The large difference between the values of $^4J_{2,Me}$ and $^4J_{3,Me}$, together with ir data, are indicative of a small contribution of intramolecular hydogen bonding to the differential stabilization of the rotamers A_i. Thus, the stability sequence of the three rotamers A_i ($i = 1-3$) for **8**, from a qualitative point of view, must be $A_3 > A_1 \geq A_2$.

When the conformational behaviours of thienyl and furylsulphonyl derivatives are compared, some differences can be observed. (1) The value of $J_{(1,OH)}$ for

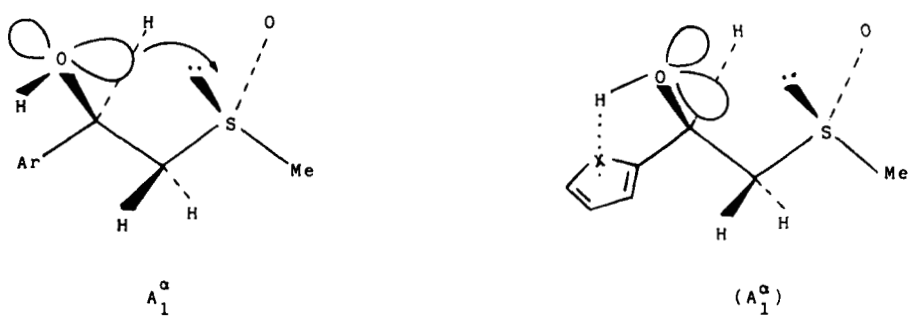


FIGURE 4 Competition between $n \Rightarrow \sigma^*_{S-R}$ stabilizing stereoelectronic interaction and (O—H . . . Ring) intramolecular association in the rotamer A_1 of the hydroxysulphoxides **6**α and **12**α.

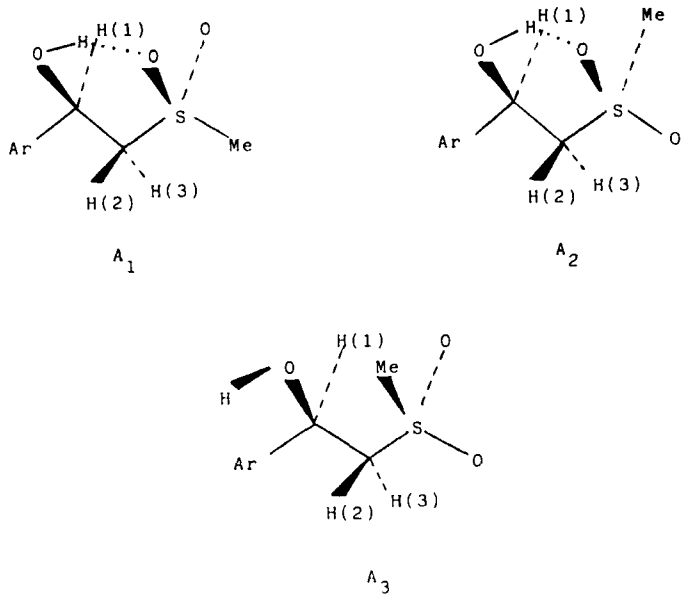


FIGURE 5 Possible *A* type rotamers for hydroxysulphones **8** and **13**.

1-(2-furyl)-2-(methylsulphonyl)ethanol (**13**) in $CDCl_3$ is higher than that of **8** (4.0 Hz and 3.2 Hz, respectively). (2) The value of $^4J_{2,Me}$ and $^4J_{3,Me}$ of **13**[2] (0.5 and 0.8 Hz, respectively) does not change when the intramolecular association is destroyed or does not exist (DMSO-d_6 as solvent or *O*-methyl derivative), while a slight increase of $^4J_{3,Me}$ (from 0.8 to 1.0 Hz) and a decrease of $^4J_{2,Me}$ (from 0.5 to 0.4 Hz) are observed for **8** in the same conditions. These differences between **8** and **13** may be attributed to the higher contribution of (O—H...O—S—O) intramolecular association in the thienyl derivative **8** [due to the stronger (OH...Ring) association for 2-furyl derivatives, as mentioned above]. Thus, whereas the relative stability of the diverse rotamers A_i do not seem to change in the furyl derivative **13**, an increase in the participation of the rotamer A_3 at expense of A_2 takes place in **8**, when intramolecular association is not operative.

EXPERIMENTAL

Melting points were determined in a Büchi apparatus and are uncorrected. Elemental analyses were performed by the Servicio de Análisis Elemental de los Servicos Técnicos de la Universidad de Granada (STRUGA) with a Perkin–Elmer model 240C analyzer.

MS data were obtained at an ionizing voltage of 70 eV on a Kratos MS-80 RFA. The more important fragments are reported in mass unit (m/z) and the values in brackets are the relative intensities from the base peak (as 100%). Ir spectra were taken with a Perkin–Elmer model 299 spectrometer. ^{1}H-nmr spectra were recorded on a Bruker WP-80-SY instrument. Shifts are reported in ppm down field from internal Me_4Si. In order to observe hydroxyl splitting, the deuterated chloroform was purified by distilling twice from phosphorous pentoxide and anhydrous potassium carbonate. The analyses of the spectra were carried out using a PANIC program on an ASPECT 2000 computer of the spectrometer. The silica gel used in chromatography was Merck F-254 (tlc) or 60 (70–230 mesh)(column).

(Methylsulphenyl)methyl 2-thienyl ketone (**1**). *n*-Butyllithium (72 mmol) is added to a stirred solution of diisopropylamine (10.3 mL, 72 mmol) in THF (60 mL) at −78°C under an atmosphere of nitrogen. After 15 minutes, the mixture is allowed to warm to −25°C and stirred for an additional period of 30 minutes at this temperature. Then a mixture of 2-acetylthiophene (30 mmol) in THF (8 mL) and HMPA (40 mL) is added, and the reaction mixture is stirred subsequently for 30 minutes at −25°C, 30 minutes at 0°C and 40 minutes at room temperature. The enolate solution is then cooled at 0°C and then dimethyl disulphide (6.35 mL, 72 mmol) is added. After stirring at room temperature for 1 h, the reaction mixture is poured into a separatory funnel containing ether and 10% aqueous hydrochloric acid. The aqueous layer is separated, and the organic phase is washed with another portion of acid and with a portion of saturated aqueous sodium hydrogen carbonate solution. The organic phase is dried over anhydrous sodium sulphate and concentrated *in vacuo* to give **1** as a solid material, that is purified by column chromatography (ether-hexane, 1:20). Yield 87%. M.p. 112–114°. ir (KBr) ν_{max}: 3090, 2910, 1635, 1410, and 745 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.58 (d, 1H, J = 1.6 Hz, C_4H_3S), 7.23 (d, 1H, J = 3.6 Hz, C_4H_3S), 6.54 (dd, 1H, J = 1.6 and 3.6 Hz, C_4H_3S), 3.58 (s, 2H, CH_2S), and 2.13 (s, 3H, SCH_3). MS, m/z: 172 (M^+) (23), 157 (2), 143 (24), 126 (10), 111 (100), and 97 (6).

(Methylsulphinyl)methyl 2-thienyl ketone (**2**). It was prepared from ethyl 2-thiophenecarboxylate and dimethyl sulphoxide,[5] yield 84%. M.p. 81–83° (from ethyl acetate). ir (KBr) ν_{max}: 3100–3010, 2950–2910, 1655, 1520, 1415, 1030, and 940 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.80 (m, 2H, J = 4.9, 3.8, and 1.1 Hz, C_4H_3S), 7.19 (dd, 1H, J = 4.9 and 3.8 Hz, C_4H_3S), 4.26 (m, 2H, CH_2SO), and 2.76 (s, 3H, $SOCH_3$). Anal. calc. for $C_7H_8S_2O_2$: C 44.64, H 4.28; found C 44.89, H 4.20.

(Methylsulphonyl)methyl 2-thienyl ketone (**3**). It was prepared by condensation of potassium dimethylsulphone carbanion with ethyl 2-thiophenecarboxylate following the procedure reported by Russel *et al.*[16] for similar compounds. Crystallized from ethyl acetate as colourless needles, yield 96%, m.p. 120–121°. ir (KBr) ν_{max}: 3100–3050, 3010, 2990, 1645, 1420, 1320, 1302, 1160, and 745 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.88–7.77 (m, 2H, C_4H_3S), 7.26–7.15 (m, 1H, C_4H_3S), 4.51 (c, 2H, J = 0.8 Hz, CH_2SO_2), and 3.14 (t, 3H, J = 0.8 Hz, SO_2CH_3). Anal. calc. for $C_7H_8O_3S_2$: C 41.15, H 3.95; found C 41.34, H 3.67.

2-(Methylsulphenyl)-1-(2-thienyl)ethanol (**4**). Method a. A solution of **2** (2.9 mmol) in THF (15 mL) was added dropwise to lithium aluminum hydride (0.235 g, 6 mmol) in anhydrous ether (5 mL). After stirring for six hours, the reaction mixture was treated with saturated ammonium chloride solution and the aqueous phase was extracted with ether. The sulphide **4** was obtained as a colourless unstable liquid after purifying by column chromatography (CH_2Cl_2/hexane, 1:3), yield 70%.

Method b: Sodium borohydride (0.190 g, 4.8 mmol) was added slowly to a solution of **1** (9.6 mmol) in methanol (15 mL). After stirring for 10 minutes, the solution was concentrated and the residuum was dissolved in water (10 mL). The resulting solution was stirred for 1 h, at room temperature and then thoroughly extracted with methylene chloride. The extracts were dried and concentrated to give **4** as a colourless liquid material that was purified by column chromatography as described above. Yield 92%. ir (film) ν_{max}: 3435, 3100–3080, 2980, 2915, 1430, 1035, and 705 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.26 (m, 1H, C_4H_3S), 7.21–6.91 (m, 2H, C_4H_3S), 5.0 (ddd, 1H, J = 8.7, 4.0, and 3.3 Hz C*H*—OH), 3.10 (d, 1H, J = 3.3 Hz, OH), 2.95 (dd, 2H, J = 4.0 and −13.8 Hz, CH_2S), 2.86 (dd, 1H, J = 8.7 and −13.8 Hz, CH_2S), and 2.13 (s, 3H, S—CH_3). MS, m/z: 174 (M^+) (12), 157 (100), 127 (10), and 62 (65).

2-(Methylsulphinyl)-1-(2-thienyl)ethanol (**6α** *and* **6β**). Compound **2** (9.6 mmol) is dissolved in methanol (15 mL) and treated with sodium borohydrate (0.190 g., 4.8 mmol). After stirring for 15 minutes, the solvent is evaporated and the resulting residuum dissolved in water (10 mL) is stirred for 1 h. The solution is thoroughly extracted with methylene chloride. The extracts are dried and concentrated to give the two diastereomeric sulphoxides **6α** and **6β**, as a colourless solid material (99.2%; 40% *α*: 60% *β*) which was resolved by column chromatography (C_6H_6/Pr^iOH/hexane, 5:1:6).

(*RS/SR*) Diastereomer **6α**, m.p. 113–114°C (from ethyl acetate). ir (KBr) ν_{max}: 3210, 2910, 1415, 1075, 1020, and 720 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.35–7.25 (m, 1H, C_4H_3S), 7.07–6.9 (m, 2H, C_4H_3S), 5.57 (ddd, 1H, J = 10.5, 2.3, and 4.4 Hz, C*H*—OH), 4.73 (dd, 1H, J = 4.4 and 0.9 Hz, OH), 3.17 (dd, 1H, J = 10.5 and −13.0 Hz, CH_2SO), 3.03 (ddd, 1H, J = 2.3, 0.9, and −13.0 Hz, CH_2SO), and 2.60 (s, 3H, $SOCH_3$). Anal. calc. for $C_7H_{10}S_2O_2$: C 44.17, H 5.30; found C 44.38, H 5.36.

(*RR/SS*) Diastereomer **6β**, m.p. 81° (from ethyl acetate-hexane). ir (KBr) ν_{max}: 3120, 1425, 1063, 990, and 720 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.28 (m, 1H, C_4H_3S), 7.08–6.92 (m, 2H, C_4H_3S), 5.61 (ddd, J = 9.0, 3.6, and 2.8 Hz, C*H*—OH), 4.40 (d, 1H, J = 2.8 Hz, OH), 3.19 (dd, 1H, J = 9.0

and −13.1 Hz, CH_2SO), 3.07 (dd, 1H, J = 3.6 and −13.1 Hz, CH_2SO), and 2.70 (s, 3H, $SOCH_3$). Anal. calc. for $C_7H_{10}S_2O_2$: C 44.17, H 5.30; found C 44.18, H 5.34.

2-(Methylsulphonyl)-1-(2-thienyl)ethanol (**8**). Sodium borohydride (0.190 g, 4.8 mmol) is slowly added to a stirred solution of **3** (9.6 mmol) in methanol (15 mL). After stirring 10 minutes, the solvent is evaporated and the residue is dissolved in water (10 mL) and stirred for 1 h. The solution is thoroughly extracted with methylene chloride, and the extracts are dried and concentrated to give a solid material that crystallizes from a mixture of ethyl acetate and hexane as colourless needles. M.p. 97–99°, yield 86%. ir (KBr) ν_{max}: 3400, 3100, 3000, 2920, 1310, 1280, 1132, 1070, 970, and 735 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.35–7.25 (m, 1H, C_4H_3S), 7.10–6.95 (m, 2H, C_4H_3S), 5.60 (ddd, 1H, J = 10.3, 1.8, and 3.2 Hz, C*H*—OH), 3.56 (m, 1H, J = 10.3, 0.6, and −14.8 Hz, CH_2SO_2), 3.28 (m, 1H, J = 1.8, 0.8, and −14.8 Hz, CH_2SO), 3.02 (m, 1H, J = 3.2 and 0.8 Hz, OH), and 3.04 (dd, 3H, J = 0.8 and 0.6 Hz, SO_2CH_3). Anal. calc. for $C_7H_{10}S_2O_3$: C 40.74, H 4.88; found C 40.98, H 4.96.

Methoxy derivatives. They were prepared by methylation of the corresponding hydoxy compounds, using the phase-transfer method described by Merz.[6]

1-Methoxy-2-(methylsulphenyl)-1-(2-thienyl)ethane (**5**). Prepared from 4 as a liquid material which was purified by column chromatography (CH_2Cl_2/hexane, 1:3), yield 98%. ir (film) ν_{max}: 3100–3060, 2980–2880, 2810, 1435, 1100, and 910 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.40–7.25 (m, 1H, C_4H_3S), 7.10–6.90 (m, 2H, C_4H_3S), 4.56 (dd, 1H, J = 7.3 and 5.7 Hz, C*H*—OCH_3), 3.31 (s, 3H, OCH_3), 2.99 (dd, 1H, J = 7.3 and −13.6 Hz, CH_2S), 2.79 (dd, 1H, J = 5.7 and −13.6 Hz, CH_2S), 2.10 (s, 3H, SCH_3). MS, m/z: 188 (M^+) (10), 173 (14), 140 (15), 127 (100), 107 (36), 97 (53), and 71 (12).

(RS/SR)-1-Methoxy-2-(methylsulphinyl)-1-(2-thienyl)ethane (**7**α). It was prepared from **6**α as colourless needles, m.p. 94–95° (from ether-hexane). Yield quantitative. ir (KBr) ν_{max}: 3100–3060, 3000–2880, 2830, 1110, 1030, and 710 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.34–7.31 (m, 1H, C_4H_3S), 7.07–6.98 (m, 2H, C_4H_3S), 4.99 (dd, 1H, J = 11.2 and 2.4 Hz, C*H*—OCH_3), 3.37 (s, 3H, OCH_3), 3.15 (dd, 1H, J = 11.2 and −13.0 Hz, CH_2SO), 3.01 (dd, 1H, J = 2.4 and −13.0 Hz, CH_2SO) and 2.63 (s, 3H, $SOCH_3$). Anal calc. for $C_8H_{12}S_2O_2$: C 47.01, H 5.92; found C 47.09, H 5.97.

(RR/SS)-1-Methoxy-2-(methylsulphinyl)-1-(2-thienyl)ethane (**7**β). It was prepared from **6**β as a colourless liquid material after column chromatography (CH_2Cl_2/hexane, 1:3). Yield 95% ir (film) ν_{max}: 3080, 3030–2970, 2820, 1440, 1375, 1130, 110, 1040, 1020, and 710 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm: 7.39–7.30 (m, 1H, C_4H_3S), 7.14–6.95 (m, 2H, C_4H_3S), 5.02 (dd, 1H, J = 7.0 and 6.2 Hz, C*H*—OCH_3), 3.31 (s, 3H, OCH_3), 3.26 and 3.08 (ddd, 2H, J = 7.0, 6.2 and −13.2 Hz, CH_2SO), and 2.26 (s, 3H, $SOCH_3$). MS, m/z: 204 (M^+) (0.4), 173 (4), 124 (100), 111 (75), 94 (92) and 81 (17).

1-Methoxy-2-(methylsulphonyl)-1-(2-thienyl)ethane (**9**). This was obtained from **8** as colourless needles. M.p. 40–42° (from ether-hexane), yield 98% ir (KBr) ν_{max}: 3100–3080, 2980–2870, 2820, 1340, 1295, 1165, 1130, 1095, 960, and 710 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 3%) δ ppm 7.39–7.30 (m, 1H, C_4H_3S), 7.11–6.94 (m, 2H, C_4H_3S), 5.04 (dd, 1H, J = 10.2 and 2.6 Hz, C*H*—OCH_3), 3.60 (m, 1H, J = 10.2, 0.4, and −15.0 Hz, CH_2SO_2), 3.17 (m, 1H, J = 2.6, 1.0, and −15.0 Hz, CH_2SO_2), 3.31 (s, 3H, OCH_3), 3.01 (dd, 3H, J = 1.0 and 0.4 Hz, SO_2CH_3). Anal. calc. for $C_8H_{12}S_2O_3$: C 43.60, H 5.49; found C 43.76, H 5.49.

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