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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 2-METHYLTHIODERIVATIVES OF 1-(2'-FURYL)ETHANOL AND THEIR O-METHYL DERIVATIVES

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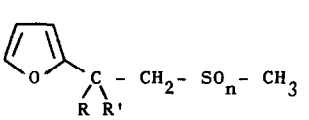
Abstract.- The synthesis and conformational analysis of some β-thioderivatives of 1-(2'-furyl)ethanol and their O-methyl derivatives, Ar-CHX-CH_2-Y (X: OH and OMe; Y: SMe, SOMe and SO_2Me), are reported. The conformational equilibria have been established from ^{1}H-nmr data and high dilution ir studies. Immunosuppressive properties of (methylsulphinyl)methyl 2-furyl ketone and 2-(methylsulphinyl)-1-(2'-furyl)ethanol, (RR/SS) and (RS/SR), have been tested.

INTRODUCTION

Recently, increasing attention has been paid to the preparation of chemicals that decrease some aspects of the immune response. Among these immunosuppressants , it is appropriate to underline the importance of oxisuran, (methylsulphinyl)methyl 2-pyridyl ketone, and some of its metabolites[1,2], whose synthesis and conformational behaviour have been studied[3]. However, the consideration of analogous compounds resulting from the substitution of the pyridyl ring by the furyl group is more interesting since these compounds are less toxic and may also show immunosuppressive activity. In this sense, we report on the synthesis of (methylsulphinyl)methyl 2-furyl ketone and those derivatives that result from reducing the carbonyl group and containing the sulphur in different oxidation states.

Scheme 1



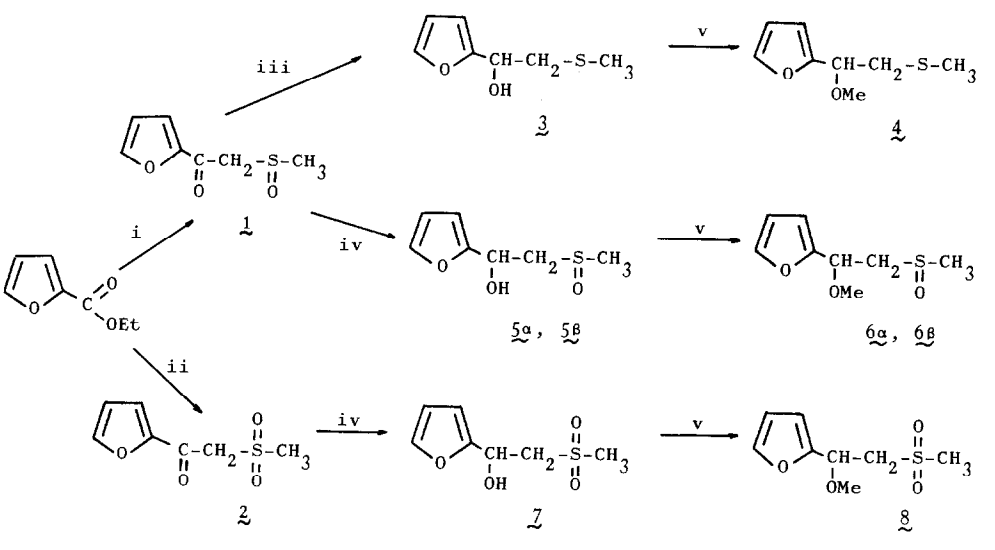
Compound	1	2	3	4	5α,5β	6α,6β	7	8
n	1	2	0	0	1	1	2	2
R			H	H	H	H	H	H
R'	=O	=O	OH	OMe	OH	OMe	OH	OMe

Taking into account the differences between pyridyl and furyl rings, it is worth studying the conformational preferences of this series of β-thioderivatives of 1-(2'-furyl)ethanol in order to asses the influence of the furyl group upon conformational stability, as well as the modifications in the immunosuppressive activity.

RESULTS AND DISCUSSION

The synthesis of 1[4] and 2 was achieved by condensation of ethyl 2-furancarboxylate with dimethylsulphinyl and dimethylsulphonyl carbanions respectively [5,6] (Scheme 2). The reaction of 1 and 2 with $NaBH_4$ yielded the corresponding hydroxyderivatives 5 and 7. The hydroxysulphoxides are obtained as a 40:60 mixture of diastereomers, 5α and 5β, which were separated by chromatography. The lowest m.p. isomer was designated as 5α. The configurational assignment has been performed by ^{1}H-nmr spectroscopy (see below) and by taking into account the synthetic route. Thus, the reduction of (R)-α-(p-tolylsulphinyl)acetophenone[7,8] with $NaBH_4$ mainly gave the diastereomer C_RS_R. In a similar way, this stereoselectivity in the (methylsulphinyl)methyl 2-furyl ketone (racemic) would lead to the enantiomer pair C_RS_S /C_SS_R in diastereomeric excess[9]. The configurational assignment of this diastereomer, denominated 5β, is in agreement with its conformational behaviour, as we will see below. Compound 3 was obtained by reduction of 1 with $LiAlH_4$. The O-methyl derivatives 4, 6α, 6β and 8 were prepared from their corresponding β-hydroxy compounds, by standard methods[10].

Scheme 2

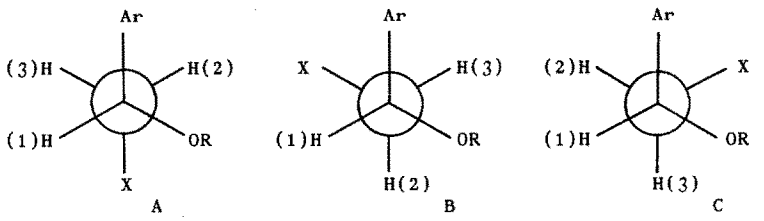


i: Bu^tOK, Bu^tOH, DMSO; ii: Bu^tOK, DMSO, $DMSO_2$; iii: $LiAlH_4$/THF; iv: $NaBH_4/H_2O$; v: $NaBH_4/Me_2SO_4$/TBAI.

The three staggered conformations resulting from $CH-CH_2$ bond rotation are depicted in Figure 1. The ^{1}H-nmr parameters of compounds 3 to 8 are collected in Table 1 and have been used to determine the conformational population for the present compounds. All the substrates have been observed in $CDCl_3$ and DMSO-d_6,

in order to examine solvent effects. In addition, the hydroxy derivatives 3, 5α, 5β and 7, where intramolecular association through hydrogen bonding is possible, have been studied at different concentrations to evaluate the role played by this association in shifting the conformational equilibria.

Figure 1 : Staggered conformations around the $CH-CH_2$ bond.



Ar= 2-Furyl; R= H, Me; X= SMe, SOMe, SO_2Me

The observed coupling constant values should correspond to a weighted mean, and the rotamer population can be calculated provided that $J^n_{i,j}$ values are known for each conformation (n= A, B and C, see Figure 1). We have calculated these values from Altona et al.'s general equation[11], using the group electronegativities calculated from Inamoto's method[12]. In order to establish the preferred conformation, it is necessary to assign H(2) and H(3) unequivocally in the ^{1}H-nmr spectra. As in similar cases[13], the assignment was carried out by using the long-range coupling constants between the methylene and the hydroxyl protons ($^4J_{3,OH}$). Thus, in compounds 3 and 5α this long-range coupling constant was observed to be 0.8 and 0.4 Hz, respectively.

Table 1 : ^{1}H-nmr parameters and conformational populations of compounds 3 - 8.

Comp.	Solv.[b]	Conc. (w/v)	Chemical Shifts (ppm) H(1)	H(2)	H(3)	SO_nMe	OR	Coupling Constants (Hz) $J_{1,2}$	$J_{1,3}$	$-J_{2,3}$	$J_{1,OH}$	Populations (%)[a] x_A	x_B	x_C
3	A[c]	10.0	4.81	2.92	2.95	2.04	d	7.1	5.4	14.0	-	47	31	21
	C	1.0	4.58	2.68	2.65	1.56	2.39	7.3	5.1	13.9	4.9	50(74)	27(14)	13(12)
	C	0.1	4.58	2.67	2.65	1.56	2.33	7.3	5.0	13.8	4.9	51	27	22
	B[e]	2.0	4.63	2.76	2.81	2.00	5.54	6.9	6.6	13.5	5.5	42(40)	45(39)	13(20)
4	A[e]	3.0	4.33	2.98	2.88	2.07	3.28	7.0	6.6	13.7	-	43(55)	46(31)	11(14)
	B[e]	3.0	4.79	2.81	2.90	2.00	3.15	7.1	6.8	13.6	-	42(49)	49(35)	9(16)
5α	A	3.0	5.33	3.25	3.04	2.65	4.46	10.1	2.6	13.1	5.0	89	0	11
	A	1.0	5.38	3.27	3.03	2.67	3.96	9.8	2.6	13.2	4.9	86(94)	0(-5)	14(11)
	A	0.1	5.41	3.29	3.01	2.69	3.45	9.5	2.5	13.2	4.6	83	-2	18
	B	1.0	4.93	3.15	2.93	2.59	5.87	10.8	2.7	13.0	5.0	96(100)	4(1)	1(-1)
6α	A	1.5	4.74	3.29	2.97	2.60	3.30	10.9	2.7	13.1	-	90(100)	3(2)	-1(-2)
	B	1.5	4.61	3.34	2.93	2.56	3.16	10.8	3.0	13.2	-	97(100)	6(3)	-3(-3)
5β	A	3.0	5.37	3.21	3.16	2.70	4.04	8.4	4.2	13.2	3.4	66	18	15
	A	1.0	5.39	3.21	3.16	2.68	3.86	8.6	4.0	13.2	3.2	68	16	16
	A	0.5	5.41	3.20	3.16	2.72	3.73	8.9	3.7	13.2	2.9	73(87)	12(0)	14(13)
	B	3.0	4.96	3.09	3.21	2.63	5.76	6.8	6.7	13.0	5.6	41(54)	48(33)	11(13)
6β	A	3.0	4.77	3.26	3.20	2.67	3.26	6.9	6.4	13.3	-	43(51)	45(35)	12(13)
	B	3.0	4.76	- 3.36 -		2.73	3.28	Deceptively simple spectrum				--(51)	--(42)	--(7)
7	A[g]	1.0	5.36	3.62	3.34	2.99	2.95	9.7	2.7	14.8	4.0	86(88)	0(-10)	13(22)
	A[h]	0.05	5.37	3.62	3.35	2.99	2.81	9.7	2.8	14.4	4.1	86	1	13
	B[i]	1.0	5.02	3.63	3.32	2.99	6.01	9.5	3.3	14.7	5.6	82(91)	8(2)	10(7)
8	A	3.0	4.79	3.70	3.20	3.00	3.30	10.1	3.0	15.0	-	89(96)	5(-3)	6(7)
	B[c]	3.0	4.71	3.84	3.38	2.95	3.17	9.4	3.7	14.8	-	80(90)	13(5)	7(7)

[a] Values in brackets correspond to the analogous 2-methylthioderivatives of 1-phenylethanol. [b] Solvents, A:$CDCl_3$, B:DMSO-d_6, C:C_6D_6. [c] Spectrum recorded at 200 MHz. [d] Broad signal. [e] Possible opposed assignation of H(2) and H(3). [f] J(3,OH)=0.4 Hz. [g] J(3,OH)=1.0 Hz, J(2,Me)=0.5 Hz, J(3,Me)=0.8 Hz. [h] J(3,OH)=0.8 Hz, J(2,Me)=0.5 Hz, J(3,Me)=0.8 Hz. [i] J(3,OH)=0.7 Hz.

The values of conformational populations for compounds 3-8 are collected in Table 1, where those for their analogous 2-methylthioderivatives of 1-phenylethanol and their O-methyl derivatives (9 - 14) are also indicated. These last values have been recalculated by us, using the previously described coupling constants [13,14] and Inamoto's electronegativities. The conformational behaviour of referable pyridyl derivatives is commented on in the text but the results are not indicated in Table 1 for the sake of brevity.

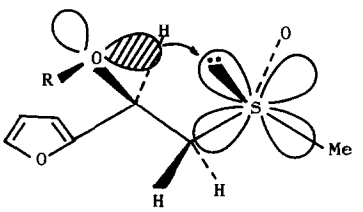
For thioethers, the most outstanding facts deduced from this table are: a) In contrast with the behaviour observed for 2-(methylsulphenyl)-1-phenylethanol 9, the rotamer population of 3 is almost independent of the solvent, x_A in $CDCl_3$ being similar to the value obtained in DMSO-d_6, where the intramolecular association must be destroyed by the solvent. b) The O-methylated furyl derivative 4, where hydrogen bonding association is not possible, shows nearly the same x_A value as 3, in contrast with their analogous hydroxyl (9) and O-methyl (10) phenyl derivatives that showed very different participations of rotamer A. The conformational behaviour for these 9 and 10 thioethers has been explained by invoking (O-H...S) intramolecular hydrogen bonding in the hydroxylated compound 9, which stabilizes the rotamer A in $CDCl_3$ (Figure 1). The situation is a little more complex for 3 because there are two hydrogen bonding possibilities: the (O-H...S) association, similar to the previous one, and the intramolecular association with the ring, (O-H...Furyl). Obviously, the first type of association is only possible in rotamers A and C, while the second one may be present in the three staggered conformations A - C. The previously commented results, gathered in Table 1, indicate the small role played by the intramolecular (O-H...S) association in the conformational equilibria of 3, in comparison with the (O-H...Furyl) hydrogen bonding. Evidence in support of this can be deduced from the $^3J_{1,OH}$ value. So, if there was an important contribution from intramolecular hydrogen bonding with the sulphenylic sulphur, the observed $^3J_{1,OH}$ should be lower than the value found (4.9 Hz), because the dihedral angle between H(1) and O-H protons would be closed to 60° [15]. Additionaly, the ir studies carried out for thioether 3 (see Table 2) showed, when diluted to 10^{-4}M in CCl_4, only 35 per cent (O-H...S) intramolecular associated molecules [16] (the intermolecular interaction must be negligible at this concentration). These results are in concordance with a not very important intramolecular association with the sulphenylic sulphur. A similar behaviour to that of 3 has recently been described for 2-(methylsulphenyl)-1-(2'-pyridyl)ethanol [3], where hydrogen bonding with the heterocycle is also operative (x_A= 57%, x_B= 16% and x_C= 28% in $CDCl_3$). The main difference between furyl and pyridyl derivatives (hydroxylated and O-methylated) corresponds to the higher participation of the conformation B for the first of them, that is, 3 and 4. The same difference is observed when furyl and phenyl derivatives are compared. The higher x_B values found for 3 and 4 may be explained taking into account the $(Ar/S)_{1,2-g}$ interaction existing in rotamers B and considering that the size of phenyl and pyridyl groups must be larger than that of furyl ring.

Table 2: O-H Stretching frecuency of compounds 3, 5α, 5β and 7.

Compound	Solv./Concent.	Free and ring associated OH stretching absorptions(cm^{-1})[16]	Intramolecular (OH...S) stretching absorption(cm^{-1})	Δν (cm^{-1})	% Intramolecular (OH...S) associated molecules. [16]
3	CCl_4/ 5.10^{-4}M	3598	3490	108	35
5α	$CDCl_3$/5.10^{-4}M	3595	--	-	0
5β	$CDCl_3$/5.10^{-4}M	3595	3400	195	65
7	$CDCl_3$/8.10^{-4}M	3590	3500	90	30

In (RR/SS) sulphoxides, 5α and 6α, the rotamer A participation is very high and independent of the solvent. The high magnitude of $^{3}J_{1,OH}$ in $CDCl_3$ (4.6-5.0Hz), typical for systems with free rotation around the C-O bond or a dihedral angle between the coupled protons of 120-130° [15], and the appearance of $^{4}J_{3,OH}$ (0.4 Hz) can only be explained by admitting a high participation of the rotamer A with the suitable stereochemistry for a "W" arrangement of the protons. The great stability of this rotamer A, shown in Figure 2, can only be explained by means of a donor--acceptor interaction between oxygen p (or sp^3) and sulphur d orbitals, strongly dependent on the relative orientation of sulphinylic oxygen [17]. Evidence in support of this n ⟶ d interaction can be found in the null proportion of (O-H...O-S) intramolecular associated molecules of 5α. Its ir spectrum in $CDCl_3$ ($c = 5.10^{-4}M$) showed only one band at 3595 cm^{-1} (Table 2)[16], revealing an important participation of a rotamer where (O-H...O-S) hydrogen bonding is not operative (rotamer A, Figure 2) . The smaller x_A value in $CDCl_3$ for the hydroxysulphoxide 5α (88%) in comparison with that for its phenyl analogue 11α (94%) may be attributed to the (O-H...Furyl) intramolecular association, that requires a suitable disposition of the hydroxylic oxygen. This arrangement makes the stabilizing donor-acceptor interaction more difficult. The analogous x_A values found for furyl and phenyl α type sulphoxides when hydrogen bondings are not feasible (i.e. hydroxylated in DMSO-d_6 and O-methylated in both solvents) is in support of this hypothesis. A similar behaviour was observed for the α diastereomer of 2-(methylsulphinyl)-1--(2'-pyridyl)ethanol, as a result of the intramolecular (O-H...Pyridyl) association (x_A= 86% in $CDCl_3$ and x_A= 99% in DMSO-d_6).

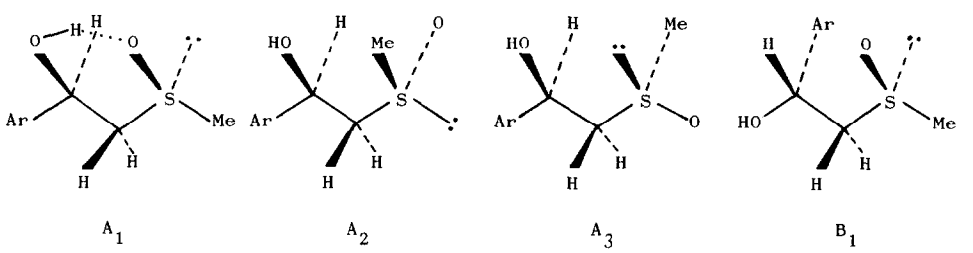
Figure 2 : Favoured rotamer A for sulphoxides 5α and 6α, stabilized by donor-acceptor n⟶d interaction.



The hydroxysulphoxide 5β, with (RS/SR) configuration, showed, as in the similar phenyl derivative [14] 11β , an important contribution of intramolecular association between hydroxyl and sulphinyl groups to the stabilization of the rotamer A. Nevertheless, as above indicated for thioether 3, there is another possibility of hydrogen bonding in 5β. An examination of the stability of the rotamers A_2 and A_3, where (O-H...Furyl) intramolecular association is possible, shows that they are not very different from A_1 , which is the only A type rotamer stabilized by (O-H...O-S) hydrogen bonding (see Figure 3). The rotamer A_3 is not very destabilized because, on the one hand, the almost non existent directional character of the sulphur lone pair [13c] reduces the importance of (OH/S) repulsive electrostatic interaction and, on the other hand, the $(Me/H)_{1,3-p}$ interaction must only be slightly destabilizing, as demonstrated for cyclic systems [18] . The rotamer A_2 has an electrostatic stabilizing $(O/H)_{1,3-p}$ interaction and an $(O/Me)_{1,3-p}$ one, that has recently been reported as not being very destabilizing in carbohydrates [19], and slightly stabilizing in other hydroxysulphoxides where an electrostatic attraction

between the hydroxylic oxygen and the methyl group of the sulphoxide, which shares the positive charge of sulphur by delocalization, is possible[20]. Futhermore, a donor-acceptor stabilizing interaction can also be operative in this rotamer. The observed conformational properties of 5β are slightly different from its analogous phenyl derivative 11β. Thus, in $CDCl_3$, the x_A value of 5β (73%) is lower than for 11β (87%) and the magnitude of $^3J_{1,OH}$ (3.5 Hz) is higher than that of the phenyl derivative (1.7 Hz). In spite of the high $^3J_{1,OH}$ value, the ir spectrum of 5β showed an important fraction of intramolecular associated molecules (see Table 2). This (O-H...O-S) intramolecular hydrogen bonding must contribute to the stabilization of rotamer A for 5β, in view of the decrease in x_A when the oxygenated function is changed (6β) or DMSO-d_6 is used as solvent (see Table 1). So, the intra-associated rotamer A_1 must be considered in the corresponding equilibria together with A_2 and A_3. These last rotamers must be responsible for the contribution of conformation A to the equilibrium, when intramolecular hydrogen bonding is not operative. The only B type rotamer to be considered is B_1, with an $(O/H)_{1,3-p}$ stabilizing interaction. This is the conformation responsible for the increase of x_B at the expense of x_A when the DMSO-d_6 proportion goes up, bringing the population values close to those of 6β. The decrease of conformational preference for rotamer A is even higher than for the analogous pyridyl sulphoxides, where the rotamer B must be more destabilizing because of the bigger size of the pyridyl ring. So, the x_A value for this compound decreases from 70% in $CDCl_3$ to 45% in DMSO-d_6 and 50% for the O-methylated derivative.

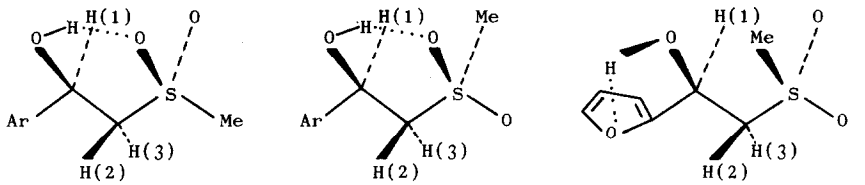
Figure 3 : Favoured rotamers for the hydroxysulphoxides denominated β, (RS/SR) configuration.



In the case of sulphones, there is a high predominance of rotamer A in the conformational equilibria of the hydroxyderivative 7 and the methyl ether 8 (Table 1). The high magnitude of $^3J_{1,OH}$ (4.1 Hz) for 7 and the appearance of $^4J_{3,OH}$ (0.8 Hz) can only be explained by admitting an important participation of the rotamer A_3, where the hydroxylic proton may be associated with the furyl ring (Figure 4). This is in agreement with the ir spectrum of 7 in $CDCl_3$ (Table 2) that showed only 30% (O-H...O-S-O) intramolecular associated molecules. The methylsulphonyl signal exhibited an additional splitting due to a long range coupling with H(2) and H(3), 0.5 Hz and 0.9 Hz respectively. The coupling constant $^4J_{3,Me}$ is considerably higher than $^4J_{2,Me}$, indicating that the rotamer A_3 predominates over A_2. These results, according to the precedents observed in similar compounds[13], may be attributed to the probable existence of an electrostatic attraction between the hydroxylic oxygen and the methyl group of the sulphone which shares the positive charge of sulphur by

delocalization [21] . The large difference between the values of $^4J_{2,Me}$ and $^4J_{3,Me}$ is indicative of a small contribution of intramolecular hydrogen bonding to the differential stabilization of rotamers around the C-S bond. Therefore, from a qualitative point of view, the stability sequence of the three rotamers for the conformation A in the sulphone 7 must be $A_3 > A_1 > A_2$. As above stated, the participation of the rotamer B for 7 and 8 is higher than that for their analogous phenyl and pyridyl sulphones, as a result of the smaller size of the furyl ring.

Figure 4 : Staggered rotamers around S-CH_2 bond for the conformer A of the sulphone 7



The evaluation of the immunosuppressive activity of compounds 1, 5α and 5β was carried out according to the previously reported procedure of cellular response test [22] , which was positive in each case (see experimental section).

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed by the "Instituto de Química Orgánica (C.S.I.C.)" at Madrid with a Perkin-Elmer model analyzer. MS data were obtained at an ionizing voltage 70eV on a AEI MS-30. The molecular ion and the base peak of each compound 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 1310 spectrometer. ^{1}H-nmr Spectra were recorded on a Bruker WS-80-SY instrument. Shifts are reported in ppm down field from internal Me_4Si. In order to observed hydroxyl splitting, the deuterated chloroform was purified by destilling twice from phosphorous pentoxide and anhydrous potasium 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).

(Methylsulphinyl)methyl 2-furyl ketone (1)

This was prepared by condensation of potassium dimethylsulphinyl carbanion with ethyl 2-furoate following the procedure reported by Russel et al.[5] for similar compounds. Yield 93%, m.p. 83-84° (lit.[4] 84.5-85°).

(Methylsulphonyl)methyl 2-furyl ketone (2)

This was prepared by condensation of potassium dimethylsulphonyl carbanion with ethyl 2-furoate following the general procedure of Russel et al.[6]. Crystallized from ethyl acetate as colourless needles, m.p. 135-137°. Yield 87%. ir, ν_{max} (KBr) : 3140, 3120, 3090, 2990, 2940, 1660, 1560, 1475, 1400, 1325, 1305, 1165 and 790 cm^{-1}.

MS, m/z: 188 $(M)^+$ (20), 95 (base peak). ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.71-7.68 (m, 1H, C_4H_3O), 7.43-7.38 (m, 1H, C_4H_3O), 6.66-6.60 (m, 1H, C_4H_3O), 4.46-4.45 (m, 2H, CH_2SO_2), 3.14-3.13 (m, 3H, SO_2CH_3). Anal. calc. for $C_7H_8O_4S$: C 44.67, H 4.28, S 17.04; found C 44.50, H 4.03, S 16.63.

2-(Methylsulphenyl)-1-(2'-furyl)ethanol (3)

A solution of 1 (0.748 g, 4.34 mmol) in 15 ml of anhydrous THF was added dropwise to lithium aluminum hydride (o.33 g, 8.69 mmol) in anhydrous ether. After stirring for six hours, the reaction mixture was treated with saturated ammonium chloride solution and the aqueous phase was extracted with ether. Concentration of the organic extracts gave a yellow oil, that was purified by column chromatography (Cl_2CH_2/ Hexane, 1:1) and yielded 0.56 g (82%) of pure sulphide 3 as a colourless unstable liquid. ir, ν_{max} (film): 3360, 3100, 2900, 1500, 1420, 1145, 1055, 1000 and 730 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ(ppm): 7.41-7.37 (m, 1H, C_4H_3O), 6.40-6.30 (m, 2H, C_4H_3O), 4.93-4.72 (m, 1H, CH), 2.99-2.91 (m, 2H, CH_2S), 2.82-2.77 (d, 1H, OH), 2.04 (s, 3H, SCH_3). MS, m/z: 158 $(M)^+$ (14), 97 (base peak).

2-(Methylsulphinyl)-1-(2'-furyl)ethanol (5α and 5β)

Compound 1 (2.50 g, 14.5 mmol) was dissolved in 20 ml of water and treated with a solution of sodium borohydride (0.30 g, 7.25 mmol) in 10 ml of water. After stirring for 90 minutes, the solution was thoroughly extracted with CH_2Cl_2 . The extracts were dried and concentrated to give 2.47 g (98%) of the two diastereomeric sulphoxides as a colourless solid. Separation of the isomers 5α and 5β was carried out by column chromatography (C_6H_6/^{i}PrOH, 19:1).

Diastereomer 5α, m.p. 66.5-68°. ir, ν_{max} (KBr): 3170, 3000, 2980, 1500, 1335, 1165, 1085, 1010 and 750 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.40-7.36 (m, 1H, C_4H_3O) , 6.40-6.31 (m, 2H, C_4H_3O), 5.44-5.22 (m, 1H, CH), 4.49-4.43 (d, 1H, OH), 3.41-2.90 (m, 2H, CH_2SO), 2.66 (s, 3H, $SOCH_3$). MS, m/z: 174 $(M)^+$ (0.3), 110 (base peak). Anal. calc. for $C_7H_{10}O_3S$: C 48.26, H 5.79, S 18.41; found C 48.49, H 5.78, S 18.13.

Diastereomer 5β, m.p. 71-72°. ir, ν_{max} (KBr): 3230, 3130, 3120, 3100, 2960, 2920, 2880, 1500, 1435, 1300, 1160, 1065, 1010, 990 and 770 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.42-7.38 (m, 1H, C_4H_3O), 6.39-6.37 (m, 2H, C_4H_3O), 5.51-5.31 (m, 2H, C_4H_3O), 3.75-3.71 (d, 1H, OH), 3.39-3.04 (m, 2H, CH_2SO), 2.77 (s, 3H, $SOCH_3$). MS, m/z: 174 $(M)^+$ (0.1), 110 (base peak). Anal. calc. for $C_7H_{10}O_3S$: C 48.26, H 5.79, S 18.41; found C 48.09, H 5.81, S 18.05.

2-(Methylsulphonyl)-1-(2'-furyl)ethanol (7)

Sodium borohydride (0.24 g, 6.1 mmol) in 5 ml of water was added slowly to 2 (1.12 g, 5.94 mmol) in 15 ml of water. After stirring for 2 hours, the solution was thoroughly extracted with chloroform. The extracts were dried and concentrated to give a solid that was crystallized from ethyl acetate as colourless needles, m.p. 81--83 °. Yield 97% (1.1 g). ir, ν_{max} (KBr): 3320, 3130, 3030, 3020, 2980, 2940, 1500, 1340, 1320, 1300, 1145, 1130 and 760 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.43-7.40 (m, 1H, C_4H_3O), 6.42-6.33 (m, 2H, C_4H_3O), 5.46-5.26 (m, 1H, CH), 3.80-3.19 (m, 2H, CH_2SO_2), 3.00-2.98 (m, 3H, SO_2CH_3), 2.90-2.85 (m, 1H, OH). MS, m/z: 190 $(M)^+$ (2), 110 (base peak). Anal. calc. for $C_7H_{10}O_4S$: C 44.20, H 5.30, S 16.86; found C 44.50, H 5.37, S 16.54.

Methoxyderivatives.-

They were prepared by methylation of the corresponding hydroxy compounds, using the phase-transfer method described by Merz[10] .

1-Methoxy-2-(methylsulphenyl)-1-(2'-furyl)ethane (4)

Prepared from 3 and purified by column chromatography (ether/hexane, 1:60). Yield 64%. ir, ν_{max} (film): 3100, 2980, 2920, 2820, 1500, 1463, 1440, 1425, 1335, 1100, 1015 and 745 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.42-7.38 (m, 1H, C_4H_3O), 6.41-6.32 (m, 2H, C_4H_3O), 4.42-4.25 (m, 1H, CH), 3.28 (s, 3H, OCH_3), 3.15-2.70 (m, 2H, CH_2S), 2.07 (s, 3H, SCH_3). MS, m/z: 172 $(M)^+$ (10), 111 (base peak)

1-Methoxy-2-(methylsulphinyl)-1-(2'-furyl)ethane (6α)

This was obtained by methylating 5α. It was then crystallized from ether as colourless needles, m.p. 65-66º. Yield 62%. ir, ν_{max} (KBr): 3130, 3100, 3000, 2980, 2930, 2910, 2870, 2815, 1500, 1150, 1100, 1050 and 770 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.45-7.42 (m, 1H, C_4H_3O), 6.38-6.36 (m, 2H, C_4H_3O), 4.83-4.66 (m, 1H, CH), 3.31 (s, 3H, OCH_3), 3.45-2.84 (m, 2H, CH_2SO), 2.62 (s, 3H, $SOCH_3$). MS, m/z: 188 $(M)^+$ (2), 124 (base peak). Anal. calc. for $C_8H_{12}O_3S$: C 51.04, H 6.43, S 17.03; found C 50.89, H 6.16, S 16.86.

1-Methoxy-2-(methylsulphinyl)-1-(2'-furyl)ethane (6β)

Prepared from 5β and purified by column chromatography (ether). It was obtained as a colourless liquid. Yield 55.5%. ir, ν_{max} (film): 3135, 3110, 2980, 2930, 2820, 1505, 1300, 1150, 1135, 1100, 1025 and 750 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.48--7.42 (m, 1H, C_4H_3O), 6.48-6.34 (m, 2H, C_4H_3O), 4.86-4.69 (m, 1H, CH), 3.26 (s, 3H, OCH_3), 3.44-3.01 (m, 2H, CH_2SO), 2.67 (s, 3H, $SOCH_3$). MS, m/z: 188 $(M)^+$ (0.6), 94 (base peak).

1-Methoxy-2-(methylsulphonyl)-1-(2'-furyl)ethane (8)

This was obtained from 7 and crystallized from cold ether as colourless needles, that melt at room temperature. Yield 84%. ir, ν_{max} (film): 3140, 3120, 2990, 2930, 2830, 1500, 1300, 1130, 1100, 960 and 750 cm^{-1}. ^{1}H-nmr ($CDCl_3$), δ (ppm): 7.46--7.42 (m, 1H, C_4H_3O), 6.43-6.34 (m, 2H, C_4H_3O), 4.87-4.71 (m, 1H, CH), 3.30 (s, 3H, OCH_3), 3.87-3.07 (m, 2H, CH_2SO_2), 3.07-2.93 (m, 3H, SO_2CH_3). MS, m/z: 204 $(M)^+$ (0.6), 124 (base peak).

Cellular response test for evaluating immunosuppressive activity[22].-

One hundred and sixty Swiss male mice were distributed in four lots, and each one of them was i.p. injected with 0.01 g of Salmonella abortus equi endotoxin (Bovine-type, Difco Corp., Detroit, Mich.) in 0.4 ml of physiological saline solution. Eleven days later, the four lots were, respectively, reinjected with 40, 20, 10 and 5 mg/Kg animal doses of the same endotoxin. Immediately, every ten mice of each lot received, respectively, the adequate doses of compounds 1, 5α and 5β (100 mg/Kg animal) and 6-mercaptopurine (14.3 mg/Kg animal), which was used for comparative purposes. The three tested compounds (1, 5α and 5β) behaved as immunosuppressors, the mortality with the different doses being 90-100%, after a week.

REFERENCES AND NOTES

1. J.S. Kazmer, P.E. Daddona, A.P. Dalke and W.N. Kelley, Biochem. Pharmacol., 32, 805 (1983).

2. G. Briziarelli, D. Abrutyn, J.A. Tornaben and E. Schwartz, Toxicol. Appl. Pharmacol., 36, 49 (1976).

3. J.L. García-Ruano, C. Pedregal and J.H. Rodríguez, Tetrahedron, 43, 4407 (1987).

4. E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 85, 1345 (1965).

5. G.A. Russell and G.J. Mikol, J. Am. Chem. Soc., 88, 5498 (1986).

6. H.D. Decker and G.A. Russell, J. Org. Chem., 28, 1896 (1963).

7. R. Annunziata, M. Cinquini and F. Cozzi, J. Chem. Soc., Perkin Trans. I, 1687 (1979).

8. G. Solladié, Chimia, 38, 233 (1984).

9. It must be noticed that CIP priority sequence for 58 is different from that for 2-p-tolylsulphinyl-1-phenylethanol.

10. A. Merz and G. Markl, Angew. Chem., Int. Ed. in Eng., 12, 345 (1973).

11. C.G.A. Haasnoot, F.A.A.M. Dedeeuw and C. Altona, Tetrahedron, 36, 2783 (1980).

12. N. Inamoto and S. Masuda, Chem. Lett., 1003 (1982).

13. a) F. Alcudia, J.L. García-Ruano, J.H. Rodríguez and F. Sánchez, Can. J. Chem., 57, 1642 (1979).

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

    c) F. Alcudia, F. Fariña, J.L. García-Ruano, J.H. Rodríguez and F. Sánchez, J. Chem. Soc., Perkin Trans. II, 564 (1979).

14. E. Brunet, J.L. García-Ruano, M.A. Hoyos, J.H. Rodríguez, P. Prados and F. Alcudia, Org. Mag. Res., 21, 643 (1983).

15. J.M. Bakke, Acta Chemica Scandinavica, B 40, 407 (1986).

16. Unfortunately, the absorptions due to the free O-H and (O-H...Furyl) intramolecular associated O-H overlap. Our ir studies on furfuryl alcohol showed only one band at 3600 cm^{-1}, corresponding to free O-H and intramolecular associated O-H stretching absorptions. This situation is analogous to that found for benzyl alcohol. See, for example A.S. Aaron in "Topic in Stereochemistry", Ed. by N.L. Allinger and J.L. Eliel, Wiley-Interscience, New York (1979). Vol. II, p. 2 and R. Laatikainen and K. Tuppurainen, J. Chem. Soc., Perkin Trans. II, 121 (1987) and references therein.

17. E. Brunet, J.L. García-Ruano, M.C. Martínez, J.H. Rodríguez and F. Alcudia, Tetrahedron, 40, 2023 (1984).

18. D.M. Frieze and S.A. Evans, J. Org. Chem., 40, 2690 (1975).

19. S.J. Angyal, J.K. Saunders, C.T. Grainger, R. LeFur and P.G. Williams, Carbohydr. Res., 150, 7 (1986).

20. a) E. Brunet, J.L. García-Ruano, J.H. García de la Vega, J.H. Rodríguez and N. Secundino, J. Mol. Struct., 144, 109 (1986).

    b) M.C. Carreño, J.L. García-Ruano, J.H. Rodríguez, M.A. Secundino and F. Alcudia, An. Quím., 78C, 374 (1982).

21. E. Brunet, J.L. García-Ruano, J.H. Rodríguez and F. Alcudia, Tetrahedron, 40, 4433 (1984).

22. A.E. Fox, J.L. Gingold and H.H. Freedman, Infection and Immunity, 8, 549 (1973).

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