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Tautomeric Equilibrium of Naphthazarin Thioderivatives

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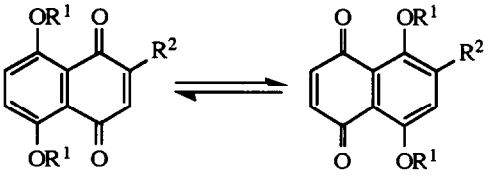
Abstract : The synthesis of p-tolylsulfenyl, p-tolylsulfinyl and p-tolylsulfonyl naphthazarins (5,8-dihydroxy-1,4-naphthoquinone) with the sulfur function on C-2 or C-6 and all their possible dimethylethers is reported. The detailed study of their ^{13}C-nmr spectra allows to establish the major presence of tautomer A in the case of naphthazarin thioether, B in the case of sulfone and a significant participation of both A and B tautomers in the sulfoxide.

Naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) and its substituted derivatives are compounds of especial interest due to their occurrence in poliketide natural products, including the anthracyclinones[1,2], aglucones of the antibiotics anthracyclines, today used in anticancer chemotherapy[2]. The synthesis of the tetracyclic hydroxyquinone framework present in these systems has been accomplished using naphthazarin derivatives via two succesive Diels-Alder cycloadditions[3] taking advantage of the tautomeric equilibrium shown in Scheme 1, which made the system a potential double dienophile. When R^1 is hydrogen or an acyl group, it can be intramoleculary transferred and the substrates exist as a mixture of tautomers in equilibrium (**A** and **B** in Scheme 1) being its composition dependent on the nature of the substituent R^2. Thus, when R^2 is an electron-withdrawing group such as methyl ketone[4] or ethoxycarbonyl group[5], only tautomer **B**, with the substituent on the aromatic ring, is present, whereas **A**, a 2-substituted quinone, is the major when R^2 is an electron donating group[4a] (Scheme 1).



R^1 = H, OAc.

R^2 = H, Ac, CO_2Et, OH, OMe, OAc, Et

Scheme 1

The presence of one or both tautomers in the equilibrium has been proposed on the basis of chemical proofs[3] and supported by trapping and isolation of derivatives of **A** and **B**[4b] where the equilibrium is "frozen". Nevertheless, as the reactivity of each tautomer could be quite different, the ratio of the derivatives obtained can never be used to ascertain accurately the composition of the tautomeric equilibrium in the precursor. ^{1}H-nmr spectroscopy has shown to be able to differentiate both tautomers when the equilibrium is frozen[4], which is the case of naphthazarin dimethylethers (R^1 = Me in Scheme 1). The low activation energy for the tautomeric exchange in naphthazarins precludes the use of low temperature nmr techniques to establish the relative ratio of each component[6]. On the other hand, criteria based on proton chemical shifts differences cannot be used due to

the similar δ values of aromatic and quinonic protons which are in addition strongly affected by the different substituents present on the naphthoquinone framework. Although there are some papers reporting ^{13}C-nmr data of naphthazarins[7], to our knowledge, nmr has never been used to evaluate the composition of the tautomeric equilibrium of any substituted naphthazarin or acyl naphthazarin. The differences in carbon chemical shifts between aromatic and quinonic carbons are higher than between the corresponding protons and the influence of the substituents on ^{13}C-δ values is lower than those observed in ^{1}H-nmr. On these basis, we could reasonably expect that ^{13}C-nmr spectroscopy were an useful tool to know the composition of the tautomeric equilibrium in naphthazarins.

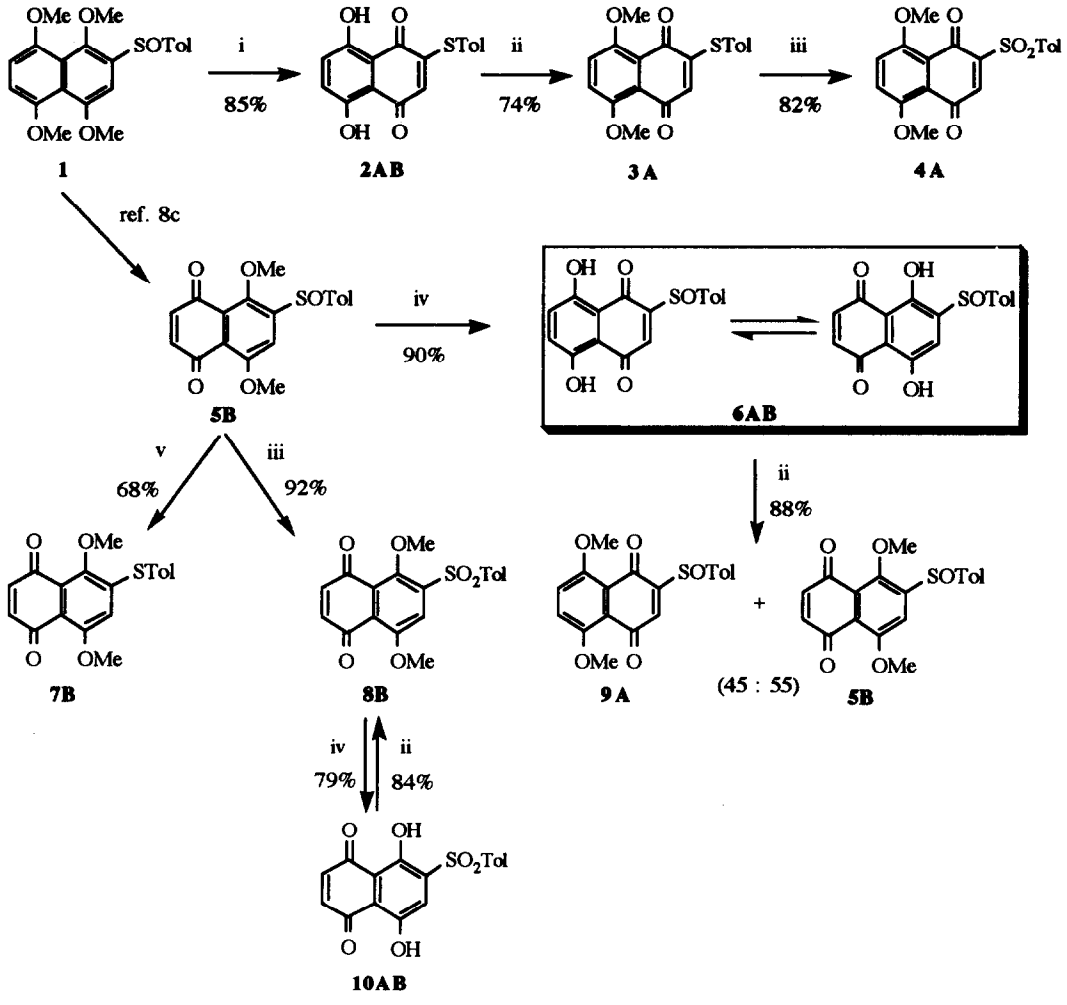
In connection with our work related to the synthesis[8a-c] and diels-Alder reactions[8a,8d] of enantiomerically pure sulfinylquinones, our interest in sulfur substituted naphthazarin derivatives was evident. The study of tautomeric equilibria in the series sulfenyl, sulfinyl and sulfonyl naphthazarins could be interesting because the electronic effect of these functions ranged from strongly withdrawing (sulfone) to donating (thioether), being the sulfinyl group intermediate in this character. We report herein the synthesis of the 2-p-tolylsulfenyl-5,8-dihydroxy-1,4-naphthoquinone (**2AB**) and the corresponding sulfoxide (**6AB**) and sulfone (**10AB**) (Scheme 2) as well as the dimethylethers of their corresponding tautomers (**3A, 4A, 9A, 5B, 7B** and **8B**) and the study of their ^{13}C-nmr behaviour, which allowed us to establish their tautomeric composition.

Naphthazarin dimethylethers exist as only one tautomer (**A** or **B** in Scheme 1) because the methyl group cannot be transferred. As these methyl groups can be easily removed with several reagents such as aluminium trichloride[9] or boron tribromide[9b], naphthazarin dimethylethers can be considered as naphthazarins with their tautomeric equilibrium frozen. This fact is of especial interest in compounds corresponding to masked forms of the less stable tautomers, which could be used to control the ring selectivity in Diels-Alder reactions of naphthazarins. We will use the notation **A** or **B** for naphthazarin dimethylethers, depending on the quinonic or aromatic structure of the ring where the sulfur function is located. In the case of hydroxyderivatives we will use the notation **AB** to indicate that both tautomers can be in equilibrium, even in those cases where actually only one of them can be detected.

The synthesis of all these compounds was carried out following the procedures indicated in Scheme 2. The oxidation of 2-p-tolylsulfinyl-1,4,5,8-tetramethoxynaphthalene **1**[8b] with cerium (IV) ammonium nitrate (CAN) afforded 6-p-tolylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (**5B**)[8b,c] which upon reaction with $AlCl_3$ in dichloromethane[9] gave sulfoxide **6AB** in 90% yield. Reduction of the sulfoxide group of **5B** with TFAA / NaI in acetone[10] gave thioether **7B**. Demethylation and concomitant reduction of the sulfinyl group was observed when compound **1** was treated with BCl_3 yielding the thioether **2AB**, whose methylation with Ag_2O / MeI[11] afforded the dimethylether **3A**. In the same conditions, sulfinyl naphthazarin **6AB** yielded a 45:55 mixture of **9A** and **5B**, that could be easily separated by chromatography. The MCPBA oxidation of thioether **3A** and sulfoxide **5B** yielded sulfonylnaphthazarin dimethylethers **4A** and **8B** respectively, whereas the sulfone **10AB** was obtained by demethylation of **8B** with $AlCl_3$. Methylation of **10AB** afforded **8B** as the only detected dimethylether.

As compound **1**, used as starting material, had been synthesized by Andersen reaction of (-)-menthyl p-toluenesulfinate with lithium-1,4,5,8-tetramethoxynaphthalene[8b], the enantiomeric excess of all the sulfoxides (**1**, **5B**, **6AB** and **9A**) had to be determined. The ^{1}H-nmr study of **9A**, in the presence of Yb(tfc)$_3$ as chiral lanthanide shift reagent, evidenced an enantiomeric excess higher than 97% (only one set of signals could be seen), indicating that this compound as well as their precursors **6AB** and **5B** were optically pure[12].

Assuming a similar reactivity of tautomers **A** and **B** with MeI / Ag_2O, the results obtained in the methylation reaction of these naphthazarins could roughly indicate the ratio of **A** and **B** in the tautomeric equilibrium. Thus, the fact that the methylation of sulfinylnaphthazarin **6AB** yielded a 45:55 mixture of dimethylethers **9A** and **5B** (resulting from the evolution of tautomers **6A** and **6B** respectively), suggested a significant participation of both tautomers in the equilibrium of **6AB**. On the other hand, the formation of only one dimethyl derivative in the methylation of sulfenyl and sulfonylnaphthazarins (**3A** from **2AB** and **8B** from **10AB**) indicated that their tautomeric equilibria were strongly shifted towards one of the tautomers, which in turn must be different in both cases.



i: BCl_3, CH_2Cl_2, r.t., 6 h; ii; MeI, Ag_2O, CH_2Cl_2, r.t., overnight; iii: MCPBA, CH_2Cl_2, r.t., 2 h; iv: $AlCl_3$, CH_2Cl_2, r.t., 1 h; v: TFAA, NaI, acetone, -40°C, 1 h.

Scheme 2

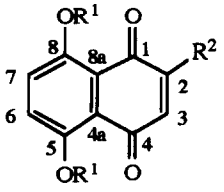
The detailed analysis of ^{13}C-nmr parameters of all these derivatives confirmed these points. ^{13}C-δ values (ppm) of the sulfur substituted naphthazarins studied are depicted in Table 1 (the signals corresponding to the p-tolyl ring, hydroxy and methoxy groups have been excluded). The carbon chemical shifts corresponding to naphthazarin dimethylether[7] (R^1 = Me, R^2 = H, **11** in Table 1) and naphthazarin[7] (R^1 = R^2 = H, **12**) are also included for comparison. The numbering of the carbons for tautomers **A** is indicated on the left of the table, whereas that of tautomers **B**, is depicted on the right. We have displayed on the same row the δ values of those carbons that could be interconverted in the tautomeric equilibria.

The higher variation of carbon chemical shifts during the tautomeric equilibration, is expected for carbons bonded to oxygen (C-1 and C-4 quinonic carbons of one tautomer are interconverted in C-5 and C-8 aromatic carbons in the other): a Δδ value higher than 25 ppm is found comparing the ^{13}C-δ values of these carbons in the frozen pairs of dimethylethers **3A-7B**, **9A-5B** and **4A-8B**. In all these naphthazarin dimethylethers (where only one tautomer is present), the chemical shifts for C-1 and C-4 remain almost constant, (> 181 ppm), regardless of the nature of the sulfur substituent and its position, whereas those of the C-5 and C-8, although dependent on the substituent, always remain lower than 157 ppm.

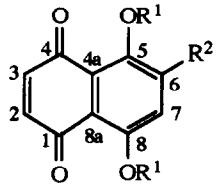
Carbon chemical shifts of the CH-CH fragment belonging to the unsubstituted ring (C-6 and C-7 in **A** are transformed in C-2 and C-3 in **B**) show Δδ values higher than 17 ppm (compare these δ values between the pairs of compounds mentioned above). Moreover, the chemical shifts of this CH-CH fragment remain almost constant around the values observed for naphthazarin dimethylether (**11**), (C-6 and C-7 appear at ca. 120 ppm in 2-substituted naphthazarin dimethylethers **A** and C-2 and C-3 are observed at ca. 138 ppm in 6-substituted naphthazarin dimethylethers **B**). These observations show the scarce influence of the substituent on these δ values and evidence that both pair of carbons appear clearly differentiated depending on the trapped tautomer. Thus, compounds **A** (adopting the tautomeric form with the substituent on C-2) exhibit two signals between 119 and 122 ppm corresponding to C-6 and C-7, whereas compounds **B** (adopting the tautomeric form with the substituent on C-6) show two signals between 137 and 139 ppm, corresponding to C-2 and C-3.

Slightly lower, but yet significant (Δδ = 14-16 ppm) is the variation of δ values of the CH in α position with respect to the sulfur substituent (C-3 in **A** is transformed in C-7 in **B**), which is partially influenced by the nature of the function. The difference in δ values of C-8a and C-4a is lower than 9 ppm and again dependent on the substituent.

Table 1. ^{13}C-nmr chemical shifts (ppm) of naphthazarins and naphthazarin dimethylethers.



A



B

R1 R2	Me H **11**[a]	Me STol **(3A)**	Me SOTol **(9A)**	Me SO_2Tol **(4A)**	H STol **(2AB)**	H H **12**[a]	H SOTol **(6AB)**	H SO_2Tol **(10AB)**	Me STol **(7B)**	Me SOTol **(5B)**	Me SO_2Tol **(8B)**	R1 R2
C-1[b]	184.0	182.0	182.6	183.1	184.4	172.9	172.6	158.1	148.8	149.2	151.1	C-5[b]
C-2	137.6	153.6	154.1	154.0	157.8	135.5	152.8	145.4	147.7	149.1	144.8	C-6
C-3	137.6	128.4	133.9	135.0	128.2	135.5	129.6	131.1	114.7	113.9	118.8	C-7
C-4[b']	184.0	181.7	181.0	182.0	184.0	172.9	172.2	160.2	156.3	157.1	155.2	C-8[b']
C-5[c]	152.9	153.6	154.3	154.5	159.0	172.9	172.0	183.6	183.7	183.9	183.2	C-1[c]
C-6[d]	119.9	121.3	121.5	121.6	130.8	135.5	134.9	138.2	139.4	139.3	137.8	C-2[d]
C-7[d']	119.9	119.6	120.4	120.1	128.6	135.5	134.4	138.5	137.1	137.4	138.6	C-3[d']
C-8[c']	152.9	154.3	155.8	155.6	158.1	172.9	169.4	183.7	184.0	184.1	183.4	C-4[c']
C-4a[e]	120.0	120.7	121.0	121.0	111.5	111.8	112.4	114.7	128.8	125.6	126.8	C-4a[e]
C-8a[e']	120.0	120.0	120.0	120.0	111.2	111.8	112.0	113.1	124.3	122.1	124.2	C-8a[e']

a ^{13}C-nmr data taken from ref. 7.

b and b', c and c', d and d', e and e' could not be inequivocally assigned.

On the basis of the above mentioned observations we could state that for naphthazarin derivatives adopting only one tautomeric form, the diagnostic signals must be, two upper than 181 ppm and other two lower than 157 ppm (corresponding to the oxygenated carbons). On the contrary, a significant contribution of both tautomers to the equilibrium would be recognized by the fact that the four signals corresponding to the oxygenated carbons (C-1, C-4, C-5 and C-8) would appear between 181 and 157 ppm (the lower the difference between them, the more similar the participation of both tautomers).

Moreover, these substrates would exhibit two signals between 119-122 or 137-140 ppm, depending on whether **A** or **B** were the favoured tautomers: the larger nearness to one of these values would indicate the nature of the predominant tautomer. In other words, the higher the participation of both tautomers in the equilibrium, the lower the difference between the ^{13}C-δ values of the aromatic and quinonic oxygenated carbons and the CH-CH unsubstituted fragment (C-6, C-7, C-2 and C-3).

In order to check if these observations are valid for naphthazarins (which have OH groups instead of OMe ones), we can compare in Table 1 the ^{13}C-δ values of naphthazarin dimethylether (**11**) (only one tautomeric form) with those of the naphthazarin (**12**) (equimolecular amount of both tautomers). Compound **11** shows two signals (two carbons each one) for the oxygenated carbons: C-1 and C-4 appear higher than 181 ppm (184.0) and C-5 and C-8 lower than 157 ppm (152.9) and other two for the four carbons corresponding to the unsubstituted CH-CH fragments existing in these compound, C-6 and C-7 at 119.9 and C-2 and C-3 at 137.7 ppm, whose chemical shifts agree with those expected for compounds where only one tautomer is present. Naphthazarin (**12**) shows only one signal for all oxygenated carbons (172.9 ppm) and other for those of the CH-CH fragments (135.5 ppm), the position of which are the expected from the above observations if there is a 1:1 mixture of tautomers in fast equilibrium. Nevertheless, the substitution of the OMe group by the OH one has certain influence on the chemical shifts of the carbons which must be taken into account when the above observations are applied to evaluate the tautomeric equilibria of naphthazarins. This effect can be estimated as $\Delta\delta = 4.5$ for oxygenated carbons and 6.8 for those of CH-CH fragment, from the comparison of the data obtained for naphthazarin (**12**) and those calculated as the average for the corresponding carbons in naphthazarin dimethylether (**11**) by assuming that the methyl group was interchangeable[13] (see Table 1).

Now, we will consider the ^{13}C-δ values obtained for sulfur substituted naphthazarins **2AB**, **6AB** and **10AB** depicted in Table 1. The application of the above observations suggests that tautomeric equilibria of compounds **2AB** and **10AB** must be quite shifted towards one of the tautomers (in both cases, two signals upper than 183 and other two lower than 160 ppm are observed for the oxygenated carbons). **B** must be the favoured tautomer in the case of sulfone **10AB** (two signals upper 138 ppm corresponding to the quinonic CH-CH fragment), and **A** in the case of thioether **2AB** (such signals appear lower than 131 ppm and are assigned to the aromatic C-6-C-7 fragment). As we can see, the δ values of oxygenated carbons in naphthazarin dimethylethers can also be used to evaluate the tautomeric equilibria in naphthazarins. The values concerning the CH-CH fragment in **A** tautomers show some deviations from the expected behaviour: the signals appear lower than 131 ppm in naphthazarins but lower than 122 ppm in dimethylethers.

In contrast with the situation observed for thioether and sulfone, the ^{13}C-δ values obtained for the sulfinyl derivative **6AB** indicate the presence of both tautomers in the equilibrium in a similar ratio: four signals corresponding to the oxygenated carbons appear between 172.6 and 169.4 ppm and other two corresponding to the CH-CH fragment at 134.9 and 134.4, which is almost the average between the observed values for thioether **2AB** (only tautomer **A**) and sulfone **10AB** (only tautomer **B**).

In conclusion, we have stated a convenient method based on ^{13}C-nmr parameters to ascertain the qualitative composition of the tautomeric equilibria in naphthazarin thioderivatives which agree with the results obtained from methylation of the precursors 5,8-dihydroxy-1,4-naphthoquinones with Ag_2O / MeI. Thus, donating electron groups such as STol, favour **A** tautomers, whereas **B** ones are predominant when electron withdrawing groups, like SO_2Tol, are present. The influence of the SOTol group on the composition of the tautomeric equilibrium (both tautomers are present) suggests that its known electron withdrawing character, favouring tautomers **B**, must be compensed by other factors, probably electrostatic, that are able to stabilize tautomers **A**.

Experimental Section

Melting points were obtained in open capillary tubes and are uncorrected. IR spectra are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded at 200.1 and 50.3 MHz in $CDCl_3$. All reactions were monitored by thin layer chromatography that was performed on precoated sheets of silica gel 60 and flash column chromatography was done with silica gel 60 (230-400 mesh) of Macherey-Nagel. Eluting solvents are indicated in the text. Apparatus for inert atmosphere experiments were dried by flaming in a stream of dry argon. CH_2Cl_2 was dried over P_2O_5. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2 and solvent dryness with Na_2SO_4.

General Procedure for $AlCl_3$ Demethylation Reactions. Method A. A solution of the corresponding naphthazarin dimethylether (2.5 mmol) in 50 mL of dry CH_2Cl_2 was added to $AlCl_3$ (3.0 g, 22.5 mmol) in 10 mL of dry CH_2Cl_2 under argon and stirred for 1 h at r.t. The reaction mixture was hydrolyzed with 10% HCl and extracted with hot $CHCl_3$ overnight. The resulting naphthazarins were obtained after evaporation of the solvent and purified by crystallization.

General Procedure for Methylation Reactions. Method B. A suspension of the corresponding naphthazarin (0.5 mmol), MeI (1.40 mL, 22.4 mmol) and Ag_2O (1.50 g, 6.4 mmol) in 20 mL of dry CH_2Cl_2 was stirred at r.t. overnight maintening the flask reaction in the dark. The resulting naphthazarin dimethylethers were obtained after filtration and evaporation of the solvent and purified by flash chromatography.

General Procedure for Sulfide to Sulfone Oxidation. Method C. To a solution of the sulfide (0.3 mmol) in 5 mL of $CHCl_3$ was added MCPBA 50-60% (225 mg, 0.6 mmol) in 10 mL of $CHCl_3$. After 2 h at r.t. the mixture was washed with $NaHCO_3$ sat. and extracted several times. After workup the sulfone was obtained and purified by crystallization.

2-*p*-Tolylsulfenyl-5,8-dihydroxy-1,4-naphthoquinone (2AB). To a solution of 2-*p*-tolylsulfinyl-1,4,5,8-tetramethoxynaphthalene[8b,c] (1) (190 mg, 0.49 mmol) in 10 mL of dry CH_2Cl_2 a solution of BCl_3 1M in CH_2Cl_2 (5 ml, 5 mmol) was added under argon. After 6 h at r.t. the reaction mixture was hydrolyzed with 10% HCl and extracted with $CHCl_3$. After workup, compound **2AB** was obtained (85% yield): mp 168-170°C (acetone); IR (KBr) 3350, 1735, 1080, 1025, 810; ^1H-NMR δ 2.44 (3H, s, CH_3Ar), 6.11 (1H, s, H_3), 7.21 and 7.28 (2H, AB system, J = 9.1 Hz, H_6 and H_7), 7.32 and 7.42 (4H, AA´BB´ system, tolyl group), 12.21 and 12.58 (2H, 2s, OH); ^{13}C-NMR 21.4, 111.2, 111.5, 123.0, 128.2, 128.6, 130.8, 131.3 (2C), 135.5 (2C), 141.2, 157.8, 158.1, 159.0, 184.0, 184.4; Anal. Calcd for $C_{17}H_{12}SO_4$: C, 65.38; H, 3.85. Found: C, 65.21; H, 4.10.

2-*p*-Tolylsulfenyl-5,8-dimethoxy-1,4-naphthoquinone (3A). Compound **3A** was obtained from **2AB** following method B after flash chromatography (ether) (74% yield): mp 213-4°C (methanol); IR (KBr) 1655, 1080, 1020, 815; ^1H-NMR δ 2.39 (3H, s, CH_3Ar), 3.90 and 3.95 (6H, 2s, OCH_3), 5.94 (1H, s, H_3), 7.26 and 7.31 (2H, AB system, J = 9.6 Hz, H_6 and H_7), 7.24 and 7.37 (4H, AA´BB´ system, tolyl group); ^{13}C-NMR 21.3, 56.8, 56.9, 119.6, 120.0, 120.7, 121.2, 124.3, 128.4, 130.9 (2C), 135.5 (2C), 140.5, 153.6, 154.3, 156.1, 181.7, 182.0; Anal. Calcd for $C_{19}H_{16}SO_4$: C, 67.04; H, 4.74. Found: C, 66.85; H, 4.90.

2-*p*-Tolylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (4A). Compound **4A** was obtained from **3A** following method C (82% yield): mp 235-6°C (methanol); IR (KBr) 1650, 1310, 1150; ^1H-NMR δ 2.46 (3H, s, CH_3Ar), 3.82 and 3.88 (6H, 2s, OCH_3), 7.21 and 7.26 (2H, AB system, J = 9.4 Hz, H_6 and H_7), 7.60 (1H, s, H_3), 7.40 and 8.06 (4H, AA´BB´ system, tolyl group); ^{13}C-NMR 21.5, 56.6, 56.9, 120.1, 120.5, 121.5,

121.6, 129.0 (2C), 129.5 (2C), 135.0, 136.9, 141.4, 154.0, 154.5, 155.6, 182.0, 183.1; Anal. Calcd for $C_{19}H_{16}SO_6$: C, 61.28; H, 4.33. Found: C, 61.07; H, 4.40.

6-*p*-Tolylsulfenyl-5,8-dimethoxy-1,4-naphthoquinone (7B). A solution of trifluoroacetic anhydride (0.2 mL, 2.5 mmol) in 1 mL of acetone was added dropwise into a stirred suspension of compound **5B**[8b,c] (178 mg, 0.5 mmol) and sodium iodide (225 mg, 1.5 mmol) in 5 mL of acetone at -40°C under argon. After 1 h at this temperature an excess of saturated aqueous Na_2SO_3 and Na_2CO_3 was added. After workup and flash chromatography (ether:hexane 3:1) compound **7B** was obtained (68% yield): mp 165-6°C (methanol); IR (KBr) 1655, 1075, 1025, 820; ^{1}H-NMR δ 2.43 (3H, s, CH_3Ar), 3.59 and 3.95 (6H, 2s, OCH_3), 6.51 (1H, s, H_3), 6.73 and 6.78 (2H, AB system, J = 10.2 Hz, H_2 and H_3), 7.31 and 7.48 (4H, AA'BB' system, tolyl group); ^{13}C-NMR 21.3, 56.2, 61.2, 114.7, 116.9, 124.3, 125.5, 130.9 (2C), 135.7, 137.1, 139.4 (2C), 140.4, 147.7, 148.8, 156.3, 183.7, 184.8; Anal. Calcd for $C_{19}H_{16}SO_4$: C, 67.04; H, 4.74. Found: C, 67.12; H, 4.81.

6-*p*-Tolylsulfonyl-5,8-dimethoxy-1,4-naphthoquinone (8B). Compound **8B** was obtained from **5B**[8b,c] following method C (92% yield) and from **10AB** following method B after flash chromatography (acetone:hexane 1:2) (84% yield): mp 199-200°C (methanol); IR (KBr) 1650, 1315, 1145; ^{1}H-NMR δ 2.41 (3H, s, CH_3Ar), 3.94 and 4.10 (6H, 2s, OCH_3), 6.78 and 6.85 (2H, AB system, J = 10.2 Hz, H_2 and H_3), 7.31 and 7.85 (4H, AA'BB' system, tolyl group), 8.17 (1H, s, H_7); ^{13}C-NMR 21.4, 57.0, 63.5, 118.8, 124.2, 126.8, 128.2 (2C), 129.4 (2C), 137.0, 137.8, 138.6, 142.7, 144.8, 151.1, 155.2, 183.2, 183.4; Anal. Calcd for $C_{19}H_{16}SO_6$: C, 61.28; H, 4.33. Found: C, 61.39; H, 4.43.

6-*p*-Tolylsulfonyl-5,8-dihydroxy-1,4-naphthoquinone (10AB). Compound **10AB** was obtained from **8B** following method A (79% yield): mp 179-81°C (hexane); IR (KBr) 3320, 1605, 1320, 1150; ^{1}H-NMR δ 2.44 (3H, s, CH_3Ar), 7.06 (2H, s, H_2 and H_3), 7.34 and 7.96 (4H, AA'BB' system, tolyl group), 8.14 (1H, s, H_7), 12.12 and 12.84 (2H, 2s, OH); ^{13}C-NMR 21.7, 113.1, 114.7, 129.3 (2C), 129.6 (2C), 131.1, 136.0, 138.2, 138.5, 140.3, 145.4, 158.0, 160.0, 183.6, 183.7; Anal. Calcd for $C_{17}H_{12}SO_6$: C, 59.30; H, 3.51. Found: C, 59.41; H, 3.39.

(S)-2-*p*-Tolylsulfinyl-5,8-dihydroxy-1,4-naphthoquinone (6AB). Compound **6AB** was obtained from **5B**[8b,c] following method A (90% yield): mp 206-8°C (acetone-hexane); $[\alpha]_D^{20}$ -47° (c = 0.038, $CHCl_3$); IR (KBr) 3300, 1610, 1550, 1250, 1200, 1180, 1040; ^{1}H-NMR δ 2.38 (3H, s, CH_3Ar), 7.10 and 7.17 (2H, AB system, J = 9.9 Hz, H_6 and H_7), 7.28 and 7.70 (4H, AA'BB' system, tolyl group), 7.84 (1H, s, H_3), 12.22 and 12.38 (2H, 2s, OH); ^{13}C-NMR 21.5, 112.0, 112.4, 125.8 (2C), 129.6, 130.1 (2C), 134.2, 134.9, 139.0, 142.8, 152.8, 169.4, 172.0, 172.2, 172.6; Anal. Calcd for $C_{17}H_{12}SO_5$: C, 62.19; H, 3.66. Found: C, 62.25; H, 3.65.

(S)-6-*p*-Tolylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone[8b,c] (5B). Compound **5B** was obtained from **6AB** following method B as a 45:55 mixture of **9A** and **5B**, after flash chromatography (acetone:hexane 1:3) (50% yield). All physical and spectroscopical data were in agreement with those reported by us[8b,c].

(S)-2-*p*-Tolylsulfinyl-5,8-dimethoxy-1,4-naphthoquinone (9A). Compound **9A** was obtained from **6AB** following method B as a 45:55 mixture of **9A** and **5B** after flash chromatography (acetone:hexane 1:3) (38% yield): mp 234-5°C (ethanol); $[\alpha]_D^{20}$ -143° (c = 0.5, $CHCl_3$); IR (KBr) 1650, 1285, 1205, 1040, 915, 820; ^{1}H-NMR δ 2.36 (3H, s, CH_3Ar), 3.91 and 3.95 (6H, 2s, OCH_3), 7.29 and 7.36 (2H, AB system, J = 9.6 Hz, H_6 and H_7), 7.45 (1H, s, H_2), 7.27 and 7.74 (4H, AA'BB' system, tolyl group); ^{13}C-NMR 21.4, 56.7, 56.9, 120.4, 121.5, 126.0 (2C), 130.0 (2C), 130.1, 133.9, 139.1, 142.3, 149.8, 154.1, 154.3, 155.8, 181.0, 182.6; Anal. Calcd for $C_{19}H_{16}SO_5$: C, 64.05; H, 4.49. Found: C, 64.01; H, 5.11.

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12.- This study could not be carried out on the naphthazarin **6AB** because the signals corresponding to its racemic form were not well resolved in the presence of the chiral shift reagent.

13.- This effect must be partially attributed to the different influence of OH and OMe groups on the chemical shift of the ipso and vicinal carbons ($\Delta\delta < 3$ ppm in 1,4 dioxygenated benzenes) and to the strong hydrogen bonding of the hydroxyl groups with the carbonyl ones in naphthazarins, which would mainly affect to the carbons on the aromatic ring.

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