SYNTHESIS AND TAUTOMERISM OF 2,4-DIHYDROXYQUINOLINES

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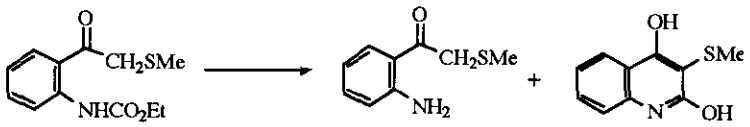
Abstract- The reaction of ethyl N-[2-(2-Z-acetyl)phenyl]carbamates with NaH/THF yields 3-Z-2,4-dihydroxyquinolines [Z=SMe, SOMe, SO_2Me and CN]. The study of the tautomeric equilibria of all these substrates by ^{13}C-nmr shows that thioether and nitrile exhibit the 2-quinolone structure, whereas the sulfoxide and probably the sulfone exist as 4-quinolone tautomers.

In previous paper[1] we have reported the anomalous behaviour of the *N*-ethylcarbamates of 1-(2-aminophenyl)-2-Y-ethanol (Y=SMe, SOMe and SO_2Me) in basic media, which did not yield the expected hydroxyamino derivatives. A similar anomalous behaviour was observed in reactions of the corresponding carbonyl derivatives. Thus, during the course of synthetic investigations involving the preparation of some oxisuran bioisosters (oxisuran = methylsulfinylmethyl 2-pyridyl ketone),[1, 2] it became necessary to hydrolize carbamate (**3**) in order to obtain the amino derivative (**7**). Surprisingly enough, in addition to the amine, a large amount of quinoline derivative (**9**) was isolated under the usual hydrolizing conditions (NaOH/MeOH-H_2O).[3](Scheme 1)



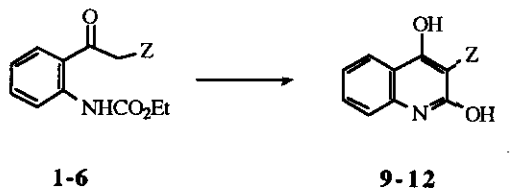
3 **7** **9**

Scheme 1

Using basic media unable to hydrolize the carbamate, it would be possible to get the 2,4-dihydroxyquinoline derivatives[4] from the more easily available *o*-acetylaniline derivatives. The importance of these heterocycles, widely spread among the quinoline type of alkaloids,[5] prompted us to investigate the scope of this reaction. Furthermore, the creation of the C(2)-

C(3) bond in quinoline can be regarded as a new approach in the creation of the quinoline ring since, to our knowledge, there is no precedent of such a process in the literature.[6]

In this paper we report the results obtained by treating the ethyl *N*-[2-(2-Z-acetyl)phenyl]carbamates [(Z=H (**1**), Br (**2**), SMe (**3**), SOMe (**4**), SO_2Me (**5**) and CN (**6**)] , shown in Scheme 2, in basic non-hydrolyzing media and the ^{13}C-nmr studies concerning the tautomeric equilibria of the obtained 3-Z-2,4-dihidroxyquinolines [Z=SMe (**9**), SOMe (**10**), SO_2Me (**11**) and CN (**12**)].

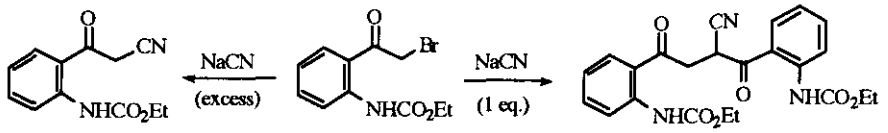


1-6 **9-12**

Z	Compound
H	**1**
Br	**2**
SMe	**3,9**
SOMe	**4,10**
SO_2Me	**5,11**
CN	**6,12**

Scheme 2

The synthesis of the compounds (**1-5**) had been previously reported.[7] The cyano derivative (**6**) was prepared by reaction of the bromo derivative (**2**) with sodium cyanide in dimethylformamide (Scheme 3). Attempts to obtain **6** failed when both starting material and reagent were used in equimolar amounts, since dimeric compound (**8**) was obtained as the major product. However, when **2** was added on a large excess of sodium cyanide, **6** could be isolated in high yield (Scheme 3).

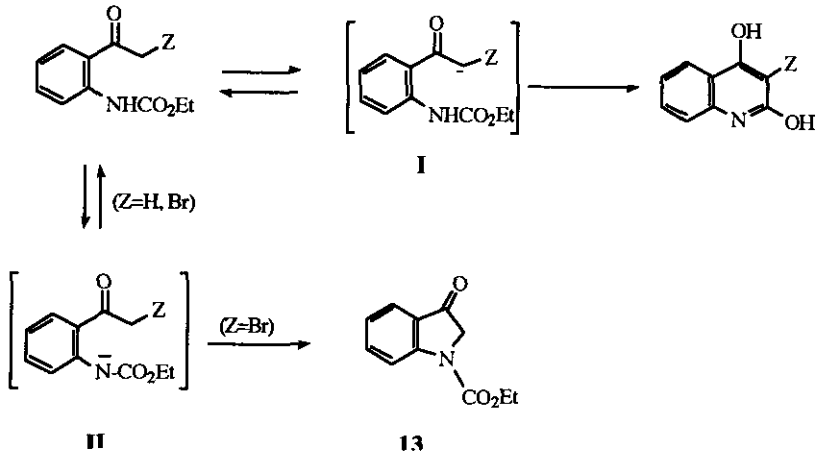


6 **2** **8**

Scheme 3

The transformation of keto derivatives (**3-6**) into 2,4-dihydroxyquinolines (**9-12**) was carried out with non-aqueous bases such as NaH/THF.[8] In these conditions hydrolysis of the carbamate group was not detected (Scheme 4). The formation of the quinoline ring requires Z to be an electron withdrawing group. This allows the generation of the intermediate anionic species (**I**), shown in Scheme 4, which undergo intramolecular attack to the carbamate group forming the C(2)-C(3) bond. On the contrary, in the case where Z does not stabilize the carbanion **I** (Z=H, Br) the formation of the carbamate anion **II** (Scheme 4) must be easier, precluding the formation of the corresponding quinoline derivatives. Thus, treatment of ethyl N-(2-acetylphenyl)carbamate **1** (Z=H) with NaH/THF recovered the starting material, whereas the ethyl *N*-(2-bromoacetylphenyl)carbamate **2** (Z=Br) yielded the indolinone (**13**) resulting of the intramolecular substitution of bromine by the carbamate anion.[1]

Once the synthesis of the 2,4-dihydroxyquinolines was optimized, we attempted the study of their tautomeric behaviour. This study was carried out by ^{13}C-nmr spectroscopy, as in similar *N*-methylated derivatives previously described.[9]

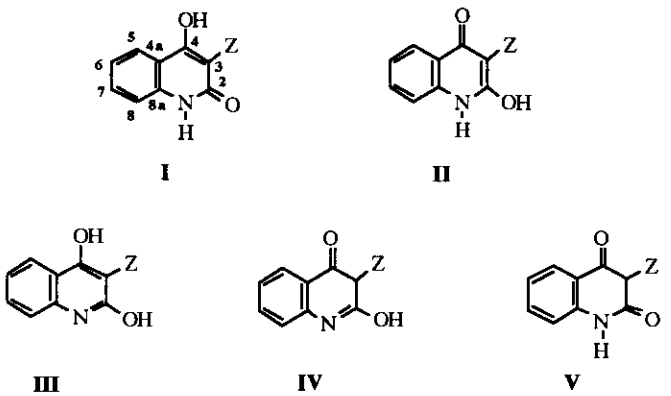


Starting Material	Reaction time (h)	Yield (%)	Reaction product
3(SMe)	2	84	**9**
4(SOMe)	120	58	**10**
5(SO_2Me)	48	80	**11**
6(CN)	72	90	**12**

Scheme 4

The five possible tautomeric forms for quinoline derivatives (**9-12**) and the numbering used to identify the carbons have been indicated in Scheme 5. The ^{13}C-chemical shifts of the signals corresponding to the commercially available 2,4-dihydroxyquinoline (Z=H) (**14**) (used as reference) and those for compounds (**9-12**), recorded in DMSO, are given in Table 1. The assignments were easily made by comparison with data reported in the literature for products of similar structure.[9, 10]

A single set of signals can be observed in the ^{13}C-nmr spectra of compounds (**9-12**) (the same is true for the ^{1}H-nmr spectra), which indicates that tautomerism showed in Scheme 5 is fast in the nmr time scale. As only one of the signals in the spectra of the compounds (**9-11**) can be assigned to saturated carbon (corresponding to the methyl group) structures IV and V can be ruled out. On the other hand, tautomer III can be also precluded because of the well-known trend of 2- and 4-hydroxypyridines and quinolines to be protonated on nitrogen as a consequence of their lower enthalpy.[11] As a result tautomerism is reduced to forms I and II.



Scheme 5

Tabla 1: ^{13}C-Nmr *chemical shifts of compounds* (**9-12**) *and* (**14**) *in* DMSO-d_6.

Compd.(Z)	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Other
9(SMe)	162.6	104.8	161.7	114.3	123.3	121.4	131.2	115.1	138.3	16.7
10(SOMe)	163.0	104.4	174.0	122.4	125.1	119.5	130.3	114.7	139.3	36.6
11(SO_2Me)	162.1	103.7	173.5	121.6	125.4	120.4	131.5	115.0	139.5	43.6
12(CN)	164.9	80.8	177.1	120.0	125.1	121.0	131.0	115.1	139.7	120.7
14(H)	163.5[a]	98.3	162.4[a]	115.1	122.6	121.0	130.8	115.2	139.2	-.-

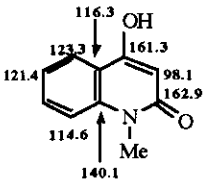
[a] Can be interchanged.

In order to know which of the two possible tautomers (2-quinolone or 4-quinolone) is mainly adopted by each of the compounds (**9-12**) described in this paper, we have used the reported chemical shifts for compounds (**15-17**)[9] collected in Scheme 6 as reference. From this Scheme it can be seen that the δ values for the atoms C-3, C-4 and C-4a are very different in both types of structures, and they must therefore be used to establish the nature of the predominant tautomer. The chemical shifts for the rest of the carbons cannot be used for this assignment because of their similarity in both tautomers.

The similarity between the observed δ values for the carbon atoms in compound (**14**) (Table 1) and those of the heterocycles (**15**) and (**16**) depicted in Scheme 6 ($\Delta\delta < 1.2$ ppm), along with the marked differences that **14** shows with respect to **17**, allow us to conclude that **14** exists mainly as the 2-quinolone tautomer. On the other hand, the comparison of the chemical shift values observed for **14** and **15** and those of **15** and **16** (all of them with 2-quinolone structure) showed respectively that neither methylation on nitrogen nor on oxygen at the 4 position changed substantially the δ values of the heterocyclic rings, at least in this kind of tautomer.

Thioether (**9**) exhibits similar chemical shifts to those of compound (**14**) (and so to those of **15** and **16**) except for C-3, which is more deshielded in **9** ($\Delta\delta$=6.5 ppm). This variation is within the range that, in other substrates,[12] a sulfenyl group

affects the chemical shifts of an olefinic carbon directly bonded to sulfur. It allows us to assume that compound (**9**) exists as 2-quinolone tautomer. Taking into account that the effect on the chemical shift of C-4a of the substitution at C-3 must be small in 4-quinolone structures, the fact that δ-C(4a) for compound (**9**) was similar to that of **14**, but very different to that of **17** (existing as 4-quinolone tautomer) reinforces the assumption of the 2-quinolone structure for thioether (**9**).



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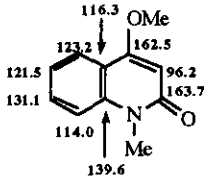

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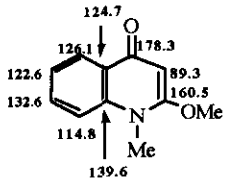

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Scheme 6

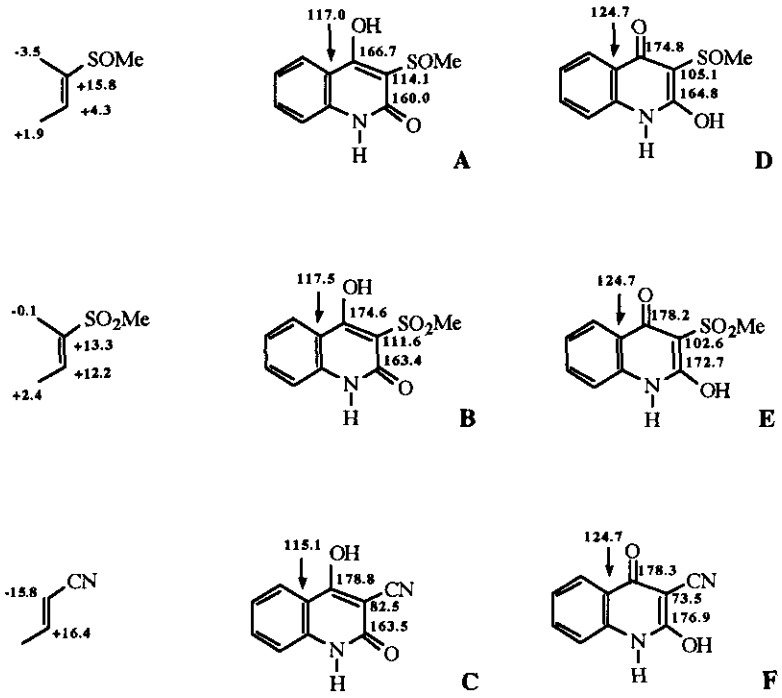
Compounds (**10**) and (**11**) show a clearly different behaviour. The β–effect resulting from one or two oxygens on sulfur atom [sulfoxide (**10**) or sulfone (**11**)], should induce a downfield shift of C-3 as compared with chemical shift of above-mentioned carbon when the oxygen is missing [sulfide (**9**)]. Nevertheless, the C-3 chemical shifts observed for **10** and **11** are even lower than those for **9** (see Table 1), which suggests that sulfoxide and sulfone must exist as a different tautomeric structure to that of **9**, namely 4-quinolone tautomer.

In order to evaluate the effect of the SOMe and SO_2Me groups on the chemical shift of the olefinic carbons, we compared the ^{13}C-chemical shifts of E-2-methylsulfinyl- and E-2-methylsulfonyl-2-butenes [obtained by treatment of an ethanolic solution of *erythro*-3-chloro (or bromo)-2-methylsulfinylbutane and *erythro*-3-chloro (or bromo)-2-methylsulfonylbutane [13] with a 10% aqueous solution of sodium hydroxide][14] with those reported for 2-butene.[15] This comparison allows us to establish the α- (on C-2), β- (on the olefinic C-3 and the saturated C-1) and γ-effects (on C-4) induced by the SOMe and SO_2Me groups shown in Scheme 7. By adding these values to those of **14**, which exhibits a 2-quinolone structure, we can calculate the expected values for **10** and **11** when they adopt the same 2-quinolone structure (A and B in Scheme 7). On the other hand on the basis of the values obtained for compound (**17**) (Scheme 6), which exibits the 4-quinolone structure,[16] it is possible to calculate the expected values for sulfoxide and sulfone, if they existed as 4-quinolone tautomer (D and E in Scheme 7).

In the case of sulfoxide (**10**), the experimental ^{13}C-δ values (Table 1) quite agree with those calculated for D, but they are very different to those calculated for A. As a consequence, we can ascertain that sulfoxide (**10**) exists as a 4-quinolone tautomer, being this compound the first non-methylated 1,4-dihydroxyquinoline reported exhibiting this structure.

In the case of sulfone (**11**), the agreement between calculated (B and E in Scheme 7) and experimental (Table 1) values is worse than in the case of sulfoxide. The 2-quinolone structure predicts better the chemical shifts of the C-2 and C-4, whereas for the 4-quinolone one, the agreement is more satisfactory for C-3 and C-4a. Although this fact prevent us from ascertaining unequivocally the favored tautomer for the sulfone (**11**), we think that it must exist as 4-quinolone, as in the

case of sulfoxide (**10**). That is because the β-effects of the sulfonyl group are very dependent on the spatial arrangement of the sulfur substituents, whereas the magnitude of the α-effects must be almost independent of such disposition, which gives higher predictive value to the first effect. Moreover, the β-effect of +12.2 ppm observed for C-3 in the 2-methylsulfonyl-2-butene (Scheme 7) is a consequence of the strong -M effect of the SO_2Me group, that requires an adequate orientation between the sulfur *d* orbitals and the double bond. The conformational restrictions around the C(3)-S bond, imposed by the oxigenated functions at C-2 and C-4 in compound (**11**), could hinder such spatial arrangement achieved, determining a much lower β-effect of the sulfonyl group than that observed in the model. These conformational restrictions must be operative in all sulfur functions, even in the case of sulfoxide, which suggests that the good agreement observed between calculated and experimental values for C-2 and specially for C-4 in compound (**10**) must be accidental. This possibility is probably due to the low magnitude of the β-effect for the SOMe group.[17]



Scheme 7

The α-effect of the CN group on an unsaturated fragment is -15.8 ppm and the β-effect is +16.4 ppm (see Scheme 7).[18] By assuming a 2-quinolone structure for **12**, we can predict the values indicated for C in Scheme 7 (taking **14** as the reference compound), whereas if the nitrile existed as 4-quinolone tautomer, it is possible to calculate the values indicated for F (taking **17** as the model compound). In this case, there is a clearly much better agreement between the experimental values and those calculated for C, which indicates that the nitrile (**12**) exists as 2-quinolone tautomer.[19] Taking into account that the CN group cannot exhibit different spatial arrangements, nor its conjugation with the double bond be can

altered by steric interactions, the β-effects predicted for this group on a simple model, must be very reliable in compound (**12**).

As conclusion, we can state that the 2-quinolone tautomer is the preferred structure for subtrates (**9**) and (**12**) as it is the case in the other 3-substituted 2,4-dihydroxyquinolines so far reported, whereas for sulfoxide (**10**) and, probably for sulfone (**11**), the predominant tautomer is 4-quinolone.

EXPERIMENTAL

Silica gel used in column chromatography was Merck-60 (230-400 mesh). Melting points were determined on a Büchi 594392 type S apparatus in open capillary tubes and are uncorrected. Mass spectra (ms) were recorded in a HP-5985 spectrometer in the electron impact (EI) at 70 eV. Mass data are reported in mass unit (m/z) and the values in brackets regard the relative intensity from the base peak (as 100%). The infrared spectra were obtained on a Nicolet 5 DX FT-IR. The proton nmr spectra were recorded on a Bruker WP-200-SY spectrometer in FT mode. Shifts are reported in ppm down field from internal TMS when deuterium chloroform was the solvent.

Ethyl N-[2-(2-cyanoacetyl)phenyl]carbamate (6). To a suspension of 0.40 g (8.20 mmol) of sodium cyanide in 30 ml of DMF 0.20 g (0.70 mmol) of ethyl *N*-[2-(bromoacetyl)pheyl]carbamate (**2**) in 10 ml of DMF were slowly added. The mixture was stirred at room temperature for 1 h, then the reaction mixture was quenched with saturated aqueous ammonium chloride. The organic phase was washed with 10 ml of water three times. The organic solution was dried over sodium sulfate. Removal of the solvent under reduced pressure furnished a residue which was crystallized from hexane/acetone. Yield 0.13 g (84%), mp 195-196°C. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.10; H, 5.24; N, 12.14. ν_{max} (KBr) 3280, 2950, 2265, 1730, 1660, 1600, 1540, 1460, 1210, 1070, 940 and 775 cm^{-1}. Ms: 232 (M^+) (20.3), 192 (19.8), 164 (14.3), 146 (100.0), 132 (14.5), 120 (63.0), 105 (6.9), 92 (55.3), 77 (11.9) and 64 (33.6). δ ($CDCl_3$): 10.70 (br s, 1H), 8.57 (m, 1H), 7.64 (m, 2H), 7.10 (m, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.18 (s, 2H) and 1.33 (t, J=7.2 Hz, 3H).

1,4-Bis(2-ethoxycarbonylaminophenyl)-2-cyano-1,4-butanedione(8). It was obtained from ethyl *N*-[2-(bromoacetyl)pheyl]carbamate in the same manner as described for the preparation of **6** but using equimolecular amount of sodium hydride. It was crystallized from hexane/methanol. Quantitative yield, mp 197-199°C. Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.61. Found: C, 63.20; H, 5.35; N, 9.62. ν_{max}(nujol) 3280, 2250, 1730, 1660, 1590, 1535, 1255, 1220, 1170, 1070 and 750 cm^{-1}. Ms: 437 (M^+) (8.9), 419 (2.6), 391 (2.8), 346 (1.3), 246 (9.7), 192 (42.3), 164 (14.1), 146 (100.0), 120 (22.6), 92 (19.5) and 65 (11.4). δ ($CDCl_3$): 10.77 (br s, 1H), 10.58 (br s, 1H), 8.60 (d, J=8.6 Hz, 1H), 8.53 (d, J=8.5 Hz, 1H), 8.08 (dd, J=1.2 and 8.2 Hz, 1H), 7.98 (dd, J=1.1 and 8.0 Hz, 1H), 7.67 (dt, J=1.2 and 8.6 Hz, 1H), 7.61 (dt, J=1.1 and 8.5 Hz, 1H), 7.20 (t, J=7.8 Hz, 1H), 7.13 (t, J=7.8 Hz, 1H), 5.08 (m, 1H), 4.23 (c, J=7.0 Hz, 2H), 4.20 (q, J=7.0 Hz, 2H), 3.90 (m, 2H), 1.30 (t, J=7.0 Hz, 3H) and 1.29 (t, J=7.0 Hz, 3H).

General procedure for the synthesis of 3-substituted 2,4-dihydroxyquinolines (9-12). To a suspension of 0.02 g (0.87 mmol) of sodium hydride in dry THF (20 ml) under argon atmosphere the corresponding carbamates (**3-6**) (0.4 mmol) in dry THF (10 ml) were added. The mixture was then refluxed. After cooling and diluting with water the solution was neutralized with 10% aqueous hydrochloric acid. In the case of the thioether (**9**) the organic material was extracted

into methylene chloride and the solution was dried over sodium sulfate. The solvent was removed under reduced pressure. In the case of the highly water-soluble quinolines (**10-12**) it was necessary to evaporate the aqueous layer to dryness and extract the solid residue with methanol.

2,4-Dihydroxy-3-methylthioquinoline (9) was obtained from **3**. Reaction time: 2 h. It was crystallized from cyclohexane/acetone, yield (84%) mp 205-207°C (decompt.). Anal. Calcd for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.83. Found: C, 57.86; H, 4.27; N, 6.88; S, 15.83. ν_{max}(KBr) 3320, 2900, 1655, 1600, 1500, 1409, 1291, 1226, 876, 750 and 630 cm^{-1}. Ms: 207 (M^+) (60.0), 192 (0.9), 174 (100.0), 164 (22.7), 146 (13.4), 133 (14.5), 120 (22.7), 104 (14.0), 92 (27.4), 77 (22.4) and 63 (18.7). δ ($CDCl_3$): 11.80 (br s, 1H), 7.96 (br s, 1H), 7.96 (dd, J=1.6 and 8.0 Hz, 1H, H-5), 7.57 (ddd, J=1.6, 7.0 and 8.2 Hz, 1H, H-7), 7.44 (dd, J=1.2 and 8.2 Hz, 1H, H-8), 7.25 (ddd, J=1.2, 7.0 and 8.0 Hz, 1H, H-6) and 2.41 (s, 3H, CH_3).

2,4-Dihydroxy-3-methylsulfinylquinoline (10) was obtained from **4**. Reaction time: 5 days. It was purified by column chromatography using methanol as eluent, yield (58%), mp >360°C. Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27; S, 14.36. Found: C, 53.78; H, 4.00; N, 6.21; S, 14.28. ν_{max}(nujol) 3409, 3219, 1665, 1623, 1264, 1166, 1025, 969, 765 and 667 cm^{-1}. Ms(EI): 223 (M^+) (43.5), 130 (43.5), 91 (52.2), 83 (69.6), 73 (100.0) and 65 (52.2). δ (DMSO-d_6): 10.20 (br s, 1H), 10.15 (br s, 1H), 7.83 (dd, J=1.6 and 8.0 Hz, 1H, H-5), 7.30 (ddd, J=1.6, 7.1 and 8.2 Hz, 1H, H-7), 7.03 (dd, J=1.1 and 8.2 Hz, 1H, H-8), 6.92 (ddd, J=1.1, 7.1 and 8.0 Hz, 1H, H-6) and 2.89 (s, 3H, CH_3).

2,4-Dihydroxy-3-methylsulfonylquinoline (11) was obtained from **5**. Reaction time: 2 days. It was crystallized from acetone/methanol, yield (80%), mp 324-326°C. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85; S, 13.40. Found: C, 50.18; H, 3.72; N, 5.81; S, 13.53. ν_{max}(nujol) 3450, 1655, 1460, 1025, 995 and 850 cm^{-1}. Ms: 239 (M^+) (4.5), 167 (22.5), 139 (63.5), 105 (87.7), 91 (24.6), 83 (32.4), 74 (23.0) 67 (21.3), 57 (67.6) and 43 (100.0). δ (DMSO-d_6): 10.20 (br s, 1H), 10.15 (br s, 1H), 7.85 (dd, J=1.6 and 8.0 Hz, 1H, H-5), 7.34 (ddd, J=1.6, 7.1 and 8.3 Hz, 1H, H-7), 7.10 (dd, J=1.2 and 8.3 Hz, 1H, H-8), 6.95 (ddd, J=1.2, 7.1 and 8.0 Hz, 1H, H-6) and 3.12 (s, 3H, CH_3).

2,4-Dihydroxy-3-cyanoquinoline (12) was obtained from **6**. Reaction time: 3 days. It was purified by column chromatography using methanol/chloroform (2/3) as eluent, yield (90%), mp 288-290°C (lit.,[20] 289°C).

ACKNOWLEDGEMENTS

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4. In order to symplify, in the first part of the paper we will refer to compounds (**9-12**) as 2,4-hidroxyquinolines even though these tautomers are not the most stable in their corresponding equilibria, as we will see in the last part.

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7. Compounds (**2-5**) were described in reference 2. Compound (**1**) had also been previously reported (F. Isikawa, Y. Watanabe, and J. Saegusa, Chem. Pharm. Bull., 1980, 28, 1357).

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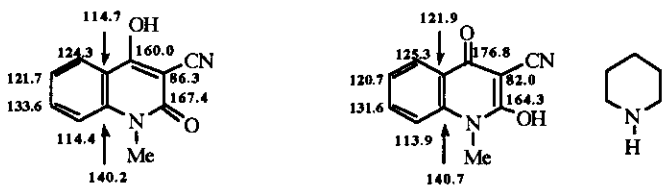
16. It is necessary to assume that *O*-methylation does not substantially modify the chemical shifts for these kind of tautomers, as it happened in the 2-quinolone ones.

17. The reported large β–effect of a thioether group on a vinylic fragment (+8 ppm, see reference 12) is not observed in compound (**9**), probably due to the mentioned conformational restrictions.

18. These values were obtained from a commercial sample of *trans*-1-cyano-2-methylethylene (Aldrich), using as base those reported for propene in reference 12, p. 132. The α–effect is very similar in the *cis* isomer (-15.4 ppm), but the β-effect is slightly higher (17.6 ppm). In the case of 2-cyanoethylene, values of -15.4 and +13.8 ppm have been respectively reported for both effects (see reference 12, p. 249 and 232).

19. The situation found for nitrile (**12**) is somehow confusing. Coppola *et al.* have described the *N*-methyl derivative of **12** and they assume a 2-quinolone structure for the free compound and the 4-quinolone form for the complex with piperidine (Scheme 8). The chemical shift values for **12** (*vide infra*) are closer to the ones reported for the "salt like" complex than to the free compound ones. This fact is very surprising since piperidine is not involved in our synthesis.



Scheme 8

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