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1-SUBSTITUTED 4-HYDROXY-3-QUINOLINESULFONIC ACIDS - PREPARATION AND STRUCTURES

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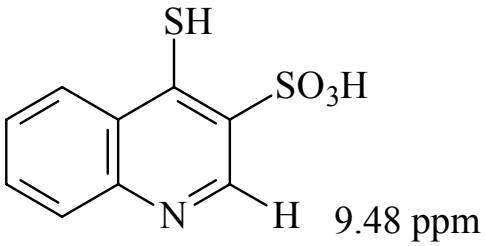
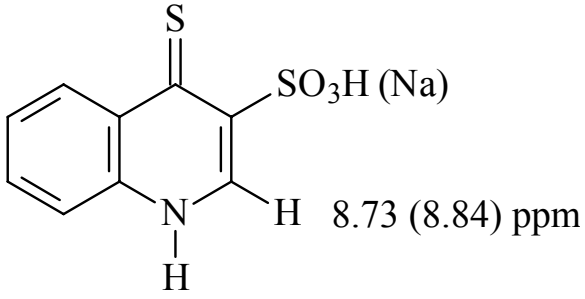
Abstract: 1-Methyl and 1-ethyl-1,4-dihydro-4-oxo-3-quinolinesulfonic acids were synthesized from 4-chloro-3-quinolinesulfonyl chloride. It was shown that the acids and their 1-H substituted analogues form a betain having a hydroxy substituent located in position 4 and a sulfonate anion group in position 3. However, the sodium salts of the acids take a form of a quinolone tautomer.

INTRODUCTION

Both in solution and solid state 2- and 4-hydroxypyridines and quinolines form almost exclusively pyridone or quinolone tautomers. Moreover, it is not often that we can isolate this tautomer that is less stable for the certain compound class. Recently, 4-mercapto-3-quinolinesulfonic acid (**1A**) and 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**1B**) have been isolated as tautomeric solids.[1] The chemical shift of H-2 in ^{1}H NMR spectra are different for these tautomers. The comparison of the shifts reveals that H-2 becomes deshielded by more than 0.75 ppm in tautomer **1A** vs. **1B**. Namely, in ^{1}H NMR spectra (DMSO-d_6) of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**1B**) this can be observed at 8.73 ppm. Similar shift (8.84 ppm) occurs in a sodium salt **1B-Na**, but not in 4-mercapto-3-quinolinesulfonic acid (**1A**), where H-2 appears at 9.48 ppm.[1]

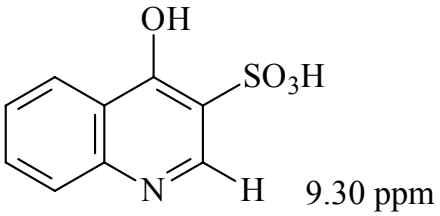


1A

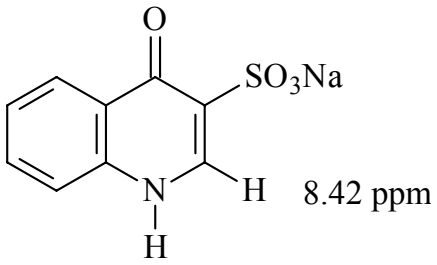


1B and **1B-Na**

We have previously hydrolyzed 4-chloro-3-quinolinesulfonyl chloride (**2**) to 1,4-dihydro-4-oxo-3-quinolinesulfonic acid assuming a priori that it takes a quinolone tautomeric form.[2,3] However, the chemical shift of H-2 in this acid appears at 9.30 ppm,[2] which seems to indicate the 4-hydroxy **3A** and not the 4-oxo **3B** form. Instead, the signal for H-2 in a sodium salt **3B-Na**, which appears at 8.42 ppm, suggests that now quinolone tautomer is formed.



3A

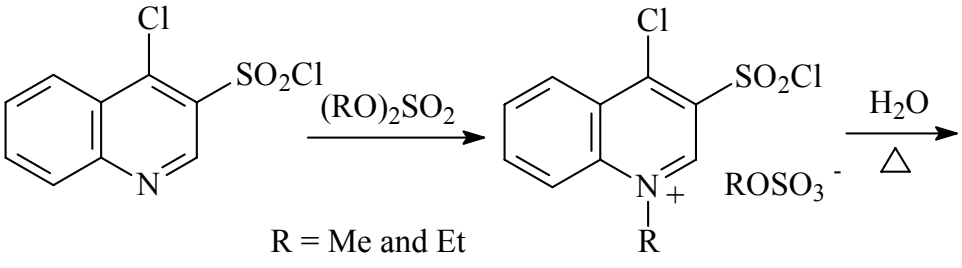


3B-Na

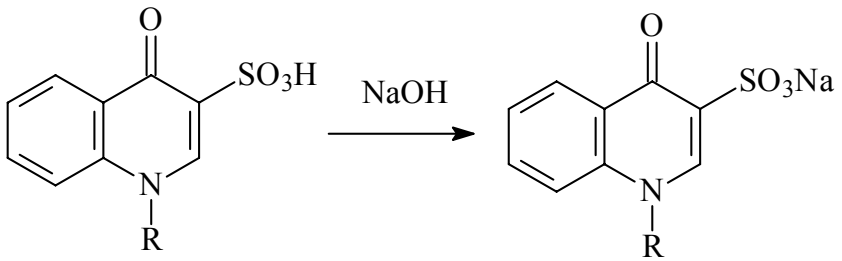
In order to prove conclusively that acid **3** takes a form of 4-hydroxyquinoline **3A** and not 4-quinolone **3B** in similar way to sodium salt **3B-Na**, we aimed the synthesis of the analogues of acid **3** which were substituted with the 1-alkyl group. We assumed that the alkylation of nitrogen N-1 should force the compound to take a quinolone form. Accordingly, the aim of the current investigations was to establish a tautomeric form of 1-substituted 1,4-dihydro-4-oxo-3-quinlinesulfonic acids (**5B**, **6B**).

RESULTS AND DISCUSSION

Acids **5B**, **6B** were synthesized by reacting 4-chloro-3-quinlinesulfonyl chloride (**2**) with dialkyl sulfate (dimethyl and diethyl) to respective quinolinium salts **4**. We used the reaction procedures described previously,[4,5] while isolated salts **4** were hydrolyzed to respective acids **5B**, **6B** with good yields (92% and 86%).



2 **4**

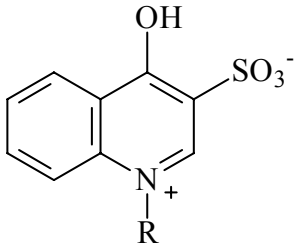


5B: R = Me, **6B**: R = Et **5B-Na**: R = Me, **6B-Na**: R = Et

The H-2 chemical shifts (DMSO-d_6) of acids **5B**, **6B** were specified below and for the comparison we also illustrate the H-2 chemical shifts of the salts **5B-Na**, **6B-Na**, respectively.

Compounds	**5B**	**6B**	**5B-Na**	**6B-Na**
δ H-2 (ppm)	9.32	9.13	8.55	8.51

This indicates that acid salts takes a form of quinolone, while 4-hydroxyquinoline tautomer is favored for the acids by themselves. The X-ray structures of the acids **5** and **6** are similar to that of 4-mercapto-3-quinolinesulfonic acid (**1A**) which forms a zwitterion:



3': R = H, **5'**: R = Me, **6'**: R = Et

Below we report the X-ray data and structures of the newly synthesized acids **3'**, **5'**, **6'**.

Figure 1. Molecular structure of **3'** and packing of the molecules in the crystal; bond lengths (Å): S(1)-O(4) 1.421(3), S(1)-O(3) 1.439(2), S(1)-O(2) 1.453(2), S(1)-C(3) 1.779(3), O(1)-C(4) 1.376(4), N(1)-C(2) 1.317(4), N(1)-C(10) 1.372(4), C(2)-C(3) 1.380(4), C(3)-C(4) 1.395(4), C(4)-C(9) 1.426(4), C(5)-C(6) 1.351(5), C(5)-C(9) 1.411(4), C(6)-C(7) 1.397(5), C(7)-C(8) 1.367(5), C(8)-C(10) 1.399(5), C(9)-C(10) 1.402(5).

Figure 2. Molecular structure of **5'** and packing of the molecules in the crystal; bond lenghts (Å): S(1)-O(4) 1.416(2), S(1)-O(3) 1.416(2), S(1)-O(2) 1.441(3), S(1)-C(3) 1.783(3), O(1)-C(4) 1.316(4), C(2)-N(1) 1.333(4), C(2)-C(3) 1.380(4), C(3)-C(4) 1.391(4), C(4)-C(9) 1.427(4), C(5)-C(6) 1.371(5), C(5)-C(9) 1.408(4), C(6)-C(7) 1.383(5), C(7)-C(8) 1.361(5), C(8)-C(10) 1.408(4), C(9)-C(10) 1.408(4), C(10)-N(1) 1.383(4), N(1)-C(11) 1.506(5).

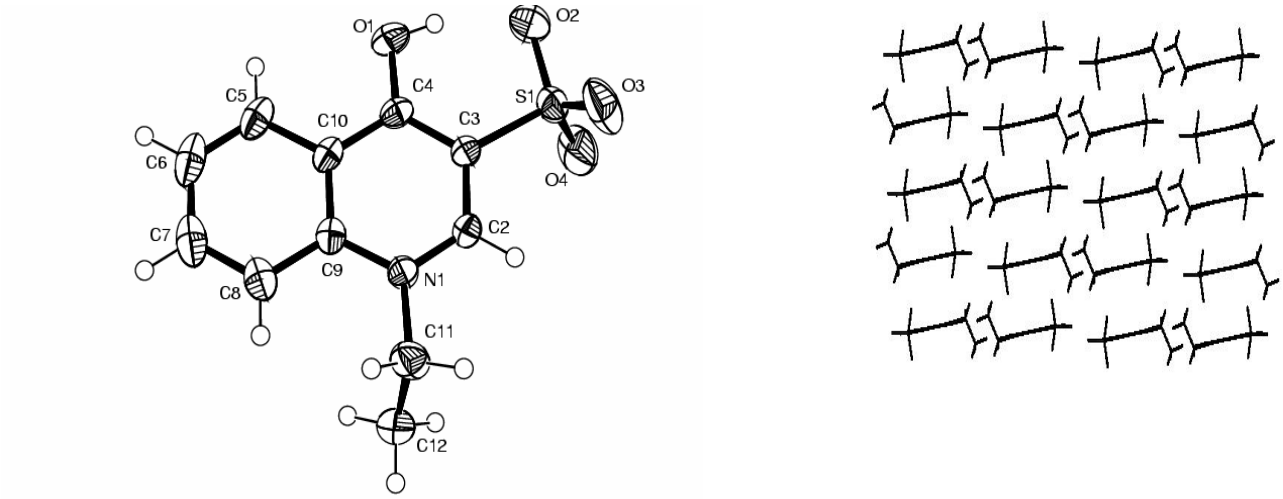


Figure 3. Molecular structure of **6'** and packing of the molecules in the crystal; bond lenghts (Å): S(1)-O(3) 1.4302(15), S(1)-O(4) 1.4305(15), S(1)-O(2) 1.4592(14), C(2)-C(3)1.3842(19), C(3)-C(4) 1.391(2), C(3)-S(1) 1.7815(15), C(4)-O(1) 1.3281(18), C(4)-C(10) 1.424(2), C(5)-C(6) 1.361(3), C(5)-C(10) 1.415(2), C(6)-C(7) 1.396(3), C(7)-C(8) 1.363(3), C(8)-C(9) 1.412(2), C(9)-C(10) 1.407(2), C(11)-C(12) 1.507(3), N(1)-C(2) 1.3282(19), N(1)-C(9) 1.388(2), N(1)-C(11) 1.484(2).

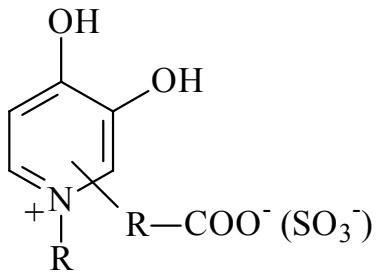
Table 1. Hydrogen bonds for 4-hydroxy-3-quinolinesulfonic acids (**3'**, **5'**, **6'**) (Å, °)

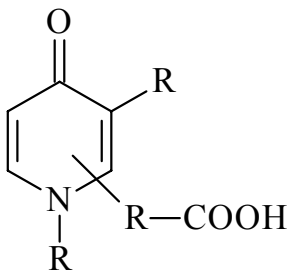
Compounds	D-H···A	D(D-H)	d(H···A)	d(DA)	<(DHA)
3'	O(1)-H(1)···O(3)-1	0.82(5)	2.13(3)	2.739(3)	131(2)
	O(1)-H(1)···O(2)	0.82(4)	2.21(5)	2.858(3)	136(4)
	N(1)-H(1)···O(2)-2	0.85(4)	1.90(4)	2.750(4)	175(3)
5'	O(1)-H(1)···O(2)	0.77(5)	1.79(5)	2.533(4)	161(5)
6'	O(1)-H(1)···O(2)	0.84(3)	1.72(3)	2.525(2)	161(3)

Symmetry equivalent positions: (1) -x, -y, -z, (2) -x, y+1/2, -z+1/2

X-Ray data clearly indicates a betaine structure of acids **3'**, **5'**, **6'**. Moreover, intramolecular hydrogen bonding between a hydrogen atom of 4-hydroxyl and at least one oxygen atom of the sulfonic group can be observed (Table 1). Additionally, intermolecular hydrogen bonding involving a hydrogen atom attached to nitrogen and an oxygen atom of sulfonic group of the second molecule is formed for nonalkylated acid **3'**. Hydrogen bonding should result in a slightly longer S-O bond (**3'** 1.453 Å, **5'** 1.441 Å, **6'** 1.459 Å) if we compare sulfonic group involved in such a bond to this unbonded (**3'** 1.421 and 1.439 Å, **5'** 1.416 Å, **6'** 1.430 Å). The comparison of the bond lenghts in Fig 1 - Fig 3 indicates that hydrogen bonding is formed for the acidic group located in *ortho* position to the hydroxyl function. A question appeared which molecular properties decide that some of 4-quinolones can also appear in a form of 4-hydroxyquinolines.

A lot of X-ray structures of 4-pyridones have been described. Some of these compounds included carboxylic or sulfonic group. Although it has not been indicted clearly, a portion of them form a zwitterionic structure with 4-hydroxygroup.[6-8] On the other hand, such a structure has not been observed for other compounds having a carboxylic or sulfonic function.[9-10] Then, what is a difference deciding the structure for these two compound groups? It appears that all compounds forming the zwitterionic structure have a hydroxy function located at the position 3 of pyridine cycle. In turn, 3-hydroxy-4-pyridones that do not have an acid group form exclusively a ketoform.[11-13]





CONCLUSIONS

It has been found that the existence of the stable 4-hydroxyquinoline tautomers of 4-quinolones is limited by the occurrence of the carboxylic or sulfonic acid group within the molecule. This observation was the same as those of 4-hydroxypyridine derivatives which was reported previously. Such a group makes possible a protonation of the oxygen atom located in the position 4. However, this alone is not sufficient to observe a formation of 4-hydroxy tautomers. Intramolecular hydrogen bonding engaging a hydrogen atom of 4-hydroxy function and an oxygen atom of the molecule is necessary for this effect. Thus, the co-occurrence of both above mentioned molecular attributes is necessary for the complete pyridine aromatization.

EXPERIMENTAL

Synthesis of 1-alkyl-4-hydroxy-3-quinolinesulfonic acids. General procedure:

A mixture of 4-chloro-3-quinolinesulfonyl chloride (**2**) (524 mg, 2 mmol) and dialkyl sulfate (1 mL) (dimethyl sulfate 10.6 mmol or dietyl sulfate 7.6 mmol) was kept at 92 ^{o}C for 2 h (dimethyl sulfate) or 5 h (dietyl sulfate). After cooling the excess of alkyl sulfate was extracted with Et_2O (3 x 5 mL), water (5 mL) was added to the resulted quinolinium salt **4** and refluxed for 1 h. The precipitate was filtered off to give of 1-methyl-4-hydroxy-3-quinolinesulfonic acid (**5'**) (440 mg, 92%) and of 1-ethyl-4-hydroxy-3-quinolinesulfonic acid (**6'**) (435 mg, 86%). The acids were recrystalized from 50% AcOH.

1-Methyl-4-hydroxy-3-quinolinesulfonic acid (**5'**): mp 306-307 ^{o}C (decomp). EI MS (15 eV), (m/z) 159(M-SO_3, 100%). ^{1}H NMR (DMSO-d_6) δ: 4.30(s, 3H, C**H**$_3$), 9.32(s, 1H, **H**2), 8.40-8.43(m, 1H, **H**5), 8.09-8.15(m, 2H, **H**7, **H**8), 7.79-7.85(m, 1H, **H**6). *Anal*. Calcd for $C_{10}H_9NO_4S$: C 50.20, H 3.79, N 5.85, S 13.40. Found: C 50.02, H 3.80, N 6.01, S 13.35.

1-Ethyl-4-hydroxy-3-quinolinesulfonic acid (**6'**): mp 299-301 ^{o}C (decomp). EI MS (15 eV), (m/z) 173(M -SO_3, 100%).^{1}H NMR (DMSO-d_6) δ: 1.45(t, *J*=7.2 Hz, 3H, C**H**$_3$CH$_2$), 4.70(q, *J*=7.2 Hz, 2H, CH$_3$C**H**$_2$), 9.13(s, 1H, **H**2), 8.33-8.42(m, 1H, **H**5), 8.14-8.17(m,1H, **H**8), 8.01-8.09(m, 1H, **H**7), 7.71-7.76(m, 1H, **H**6). *Anal*. Calcd for $C_{11}H_{11}NO_4S$: C 52.17, H 4.38, N 5.53, S 12.66. Found: C 51.91, H 4.33, N 5.87, S 12.90.

Synthesis of the sodium salts of 1,4-dihydro-4-oxo-3-quinolinesulfonic acids. General procedure:

To 4-hydroxy-3-quinolinesulfonic acid (**3'**, **5'**, **6'**) (1 mmol) 0.5 M solution of NaOH (2 mL) was added and reaction mixture was heated until solid acid sample was dissolved. Sodium salts that were formed after water evaporation, do not melt up to 330 ^{o}C. Below we specify chemical shifts δ (ppm, DMSO-*d6*) of the salts resulted, respectively:

3B-Na 8.42(s, 1H, **H**2), 8.19-8.21(m, 1H, **H**5), 7.63-7.70(m, 2H, **H**8, **H**7), 7.36-7.41(m, 1H, **H**6).

5B-Na 3.95(s, 3H, C**H**$_3$), 8.55(s, 1H, **H**2), 8.30-8.33(m, 1H, **H**5), 7.76-7.86(m, 2H, **H**8, **H**7), 7.45-7.53(m, 1H, **H**6).

6B-Na 1.35(t, *J*=7.2 Hz, 3H, CH$_2$C**H**$_3$), 4.41(q, *J*=7.2 Hz, 2H, C**H**$_2$CH$_3$), 8.51(s, 1H, **H**2), 8.27-8.29(m, 1H, **H**5), 7.75-7.83(m, 2H, **H**8, **H**7), 7.42-7.47(m, 1H, **H**6).

X-Ray analysis

All data were collected on a Nonius KappaCCD diffractometer, graphite monochromatized MoKα radiation. Structures were solved and refined using the programs SHELXS-97 [14] (Sheldrick, 1990) and SHELXL-97 [15] (Sheldrick, 1997), respectively. All non-hydrogen atoms refined anisotropically, H atoms attached to carbons attached in geometric positions and refined as 'riding' atoms, those attached to oxygens and nitrogen **3'** refined. Isotropic thermal parameters of hydrogens based upon the corresponding

bonding carbon or oxygen atom [U_{iso} = 1.2U_{eq}, U_{iso} = 1.5U_{eq} for CH_3 and OH hydrogens]. Crystal data and experimental details for structure determinations are presented in Table 2.

Table 2. Crystal data and structure refinement for reported structures.

Identification code	**3'**	**5'**	**6'**
Empirical formula	$C_9H_7NO_4S$	$C_{10}H_9NO_4S$	$C_{11}H_{11}NO_4S$
Formula weight	225.22	239.24	253.27
Temperature, (K)	293(2)	293(2)	293(2)
Crystal system, space group	Monoclinic, $P2_1/c$	Monoclinic, C2/m	Triclinic, $P\bar{1}$
Unit cell dimensions, (Å, °)	a = 9.5677(4)	a = 16.0609(9)	a = 6.7442(4)
	b = 14.3753(9)	b = 6.6007(5)	b = 8.8715(5)
	c = 7.1175(6)	c = 9.4955(5)	c = 9.7167(8)
			α = 76.642(3)
	β = 108.969(3)	β = 102.683(3)	β = 88.196(3)
			γ = 71.452(3)
Volume, ($Å^3$)	925.8(1)	982.09(11)	535.70(6)
Z, Calculated density, (g/cm^3)	4, 1.616	4, 1.618	2, 1.570
Absorption coefficient, (mm^{-1})	0.341	0.327	0.304
F(000)	464	496	252
Crystal shape	Plate	Plate	Block
Crystal size, (mm)	0.45 × 0.30 × 0.10	0.30 × 0.30 × 0.10	0.28 × 0.28 × 0.32
Crystal colour	Light yellow	Light yellow	Light yellow
θ range for data collection (°)	3.34 to 26.36	3.01 to 27.48	3.19 to 30.01
Reflections collected / unique	7355 / 1849 [R_{int} = 0.049]	3622 / 1214 [R_{int} = 0.023]	4437 / 3098 [R_{int} = 0.019]
Goodness-of-fit on F^2	1.33	1.05	1.04
Final R indices [I > 2σ(I)]	R = 0.078 WR = 0.109	R = 0.045 WR = 0.108	R = 0.046 WR = 0.112
R indices (all data)	R = 0.102 WR = 0.116	R = 0.054 WR = 0.113	R = 0.062 WR = 0.118

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