8-Quinolinolsulfonic Acids[1]

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Received April 27, 1971

The preparation of 8-quinolinol-5- and -7-sulfonic acids and their respective substitution products has been reexamined. 8-Quinolinol-7-sulfonic acid and its 5-substituted derivatives which have been reported are, in reality, 7-substituted 8-quinolinol-5-sulfonic acids. Data derived from these compounds are, consequently, also incorrect. All of the compounds in question have been prepared, and their structures were established unequivocally. The sulfonic acid group in the 7 position, as well as that in the 5 position, of 8-quinolinol is useful for blocking and unblocking those positions in synthesis.

As a result of our interest in the antifungal mechanisms of 8-quinolinol and its derivatives,[2-4] studies on methods of synthesis of these compounds have been undertaken.[5,6]

8-Quinolinol-5-sulfonic acid was first prepared by Lippmann and Fleissner,[7] and an unequivocal proof of its structure was presented by Matsumura.[8] Although 8-quinolinol-7-sulfonic acid was reported in 1906,[9] its structure was not established. That the assigned structure was correct, was questioned by Molland[10] who believed it to be the 5 isomer. Ohta and Okuda[11] also reported the preparation of 8-quinolinol-7-sulfonic acid by a modification of the earlier method.[9,12] Fujita and Goto[13] also attempted to prepare the 7-sulfonic acid by the procedure of Fritzsche.[9] With the desire to study and compare acid dissociation constants and chelate stability constants of 8-quinolinol-5- and -7-sulfonic acids with metals, Chang, *et al.*,[14] also reported the preparation of 8-quinolinol-7-sulfonic acid by a modification of the old method.[9] Srivastava and Banerji,[15] using the method of Chang, *et al.*,[14] also reported the preparation of 8-quinolinol-7-sulfonic acid.

In view of the fact that the sulfonic acid group has been found to be a convenient substituent for blocking and unblocking the 5 position of 8-quinolinol,[8,16] it was desired to examine the effectiveness of this group in the 7 position. The attempt to prepare 8-quinolinol-7-sulfonic acid by the published methods was undertaken.[9,11,14,15] In each case, a product was obtained for which the ir and nmr spectra were the same as for an authentic sample of 8-quinolinol-5-sulfonic acid. To further establish the identity of the several products, they were chlorinated and desulfonated by the method of Gershon, *et al.*,[16] and found to yield only 7-chloro-8-quinolinol, as the end material. It is apparent that in the earlier work the product of sulfonation of 8-quinolinol was not the reported 7-sulfonic acid but the 5-sulfonic acid.

The preparation of 8-quinolinol-7-sulfonic acid was achieved by sulfonation of 5-chloro-8-quinolinol, followed by removal of the chlorine by hydrogenolysis, using 10% palladium on charcoal as the catalyst. The structure for 8-quinolinol-7-sulfonic acid was established by elemental composition, as well as by the ir and nmr spectra which were consistent for the 7-sulfonic acid but different from those of 8-quinolinol-5-sulfonic acid.

In view of this finding, a review of the literature revealed a considerable number of studies which were based on what was believed to have been 8-quinolinol-7-sulfonic acid, which are incorrect.[17-25] It is further obvious that the so-called 5-substituted derivatives of what was thought to have been 8-quinolinol-7-sulfonic acid are also incorrect, as well as the data derived from these compounds.[14,15,26-29]

Since authentic 8-quinolinol-7-sulfonic acid became available, it was considered worthwhile to prepare the 5-fluoro, 5-chloro, 5-bromo, 5-nitro, and 5-amino derivatives. These reactions are summarized in Scheme I. Of the six compounds, the preparation of IIb by Riedel[30] is considered to have led to the correct product, although it was not characterized.

A further examination of the literature showed that the preparation of 7-fluoro-8-quinolinol-5-sulfonic acid from 7-amino-8-quinolinol-5-sulfonic acid by Coll and Coll[31] was found by Hollingshead[32] to lead, at best, to an impure product. The 7-fluoro derivative was pre-

(1) This work was supported in part by the U. S. Public Health Service Grant No. AI-05808.

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(11) T. Ohta and O. Okuda, *Yokugaku Zasshi*, **71**, 784 (1951).

(12) A series of 7,8-substituted derivatives was prepared subsequently, based on the sulfonic acid. A critical examination of this work revealed that none of the structures of these compounds was established, and they could just as well have been 5,8-substituted derivatives.

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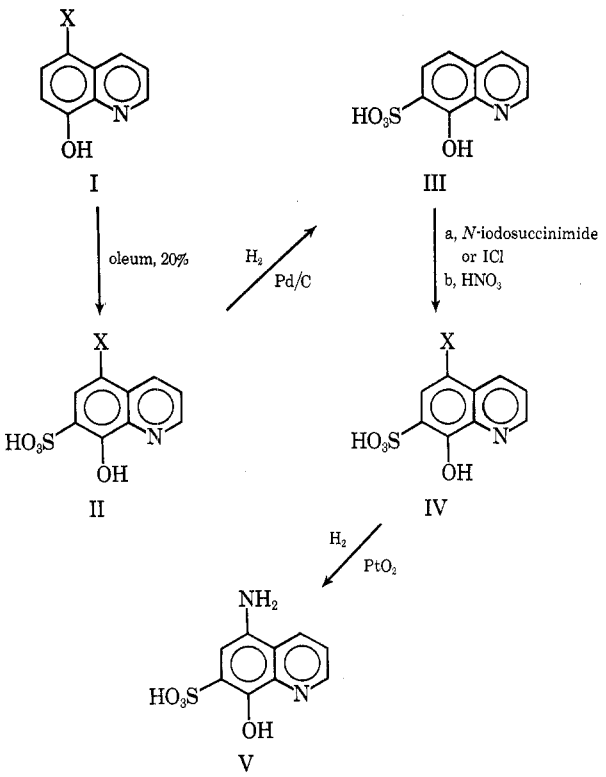
Scheme I



Ia, IIa, X = F IVa, X = I
Ib, IIb, X = Cl IVb, X = NO_2
Ic, IIc, X = Br

pared by sulfonation of 7-fluoro-8-quinolinol.[33] Since 7-amino-8-quinolinol-5-sulfonic acid, as reported by Matsumura,[8] had an incorrect elemental composition and did not agree in melting point with the corresponding product reported by Coll and Coll,[31] which was not further characterized, we obtained the compound as the hemihydrate by hydrogenation of 7-nitro-8-quinolinol-5-sulfonic acid.[5]

To complete the preparative studies of the 5-, 7-, and 5,7-sulfonic acids of 8-quinolinol, 8-quinolinol was disulfonated by a modification of the method of Claus and Posselt.[34] The isolation was simplified by crystallizing the copper(II) bischelate of the acid, followed by decomposition of the precipitate with hydrogen sulfide.

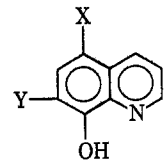
The data characterizing the new compounds are contained in Table I, and the proton chemical shifts of all the sulfonic acids are summarized in Table II. Infrared spectra for these sulfonic acids have been obtained.[35]

To determine whether the sulfonic acid group in the 7 position of 8-quinolinol can be used for both blocking and unblocking that position, 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodo-8-quinolinol-7-sulfonic acids were heated under reflux in a mixture of 15% sulfuric acid and 85% acetic acid for 24 hr, according to Gershon, *et al.*[16] 5-Fluoro-, 5-chloro-, and 5-bromo-8-quinolinols were obtained. The iodosulfonic acid yielded 8-quinolinol, as was expected, in view of the previously reported deiodination of iodonitroquinolinol.[36]

It is of interest to note that on treatment of 7-iodo-8-quinolinol-5-sulfonic acid with the sulfuric–acetic acid mixture under reflux, until the compound was just brought into solution, the products that formed were 5-iodo-8-quinolinol and 8-quinolinol. These compounds were obtained in 90% and 10% yields, respectively. The mechanism of this rearrangement is unclear.

Table I

8-Quinolinolsulfonic Acids



Compd	X	Y	Yield, %	Mp, °C[a]	Formula
III	H	SO_3H	60	274–277	$C_9H_9NO_3S$
IIa	F	SO_3H	92	351–352 dec	$C_9H_6FNO_4S$
IIb[b]	Cl	SO_3H	78	>340 dec[c]	$C_9H_6ClNO_4S$
IIc	Br	SO_3H	69	316–317 dec	$C_9H_6BrNO_4S$
IVa	I	SO_3H	89	274–275 dec	$C_9H_6INO_4S$[d]
IVb	NO_2	SO_3H	67	300 dec	$C_9H_6N_2O_6S$[e]
V	NH_2	SO_3H	78	>300 dec[c]	$C_9H_8N_2O_4S$[f]
	SO_3H	F	67	>340 dec[c]	$C_9H_6FNO_4S$
	SO_3H	NH_2	90	292–293 dec	$C_{18}H_{18}N_4O_9S_2$[g]
	SO_3H	SO_3H	85	310–315 dec	$C_9H_{11}NO_9S_2$[h]

[a] Analytical sample. Satisfactory analytical values (±0.3% for C, H, and N) were reported for all compounds (C and H only for IVb): Ed. All samples were recrystallized from 10% aqueous H_2SO_4 except 7-amino-8-quinolinol-5-sulfonic acid which was recrystallized from 1:1 aqueous DMF. [b] Compound prepared but not characterized, ref 30. [c] Indistinct decomposition point above this temperature. [d] Analysis for I satisfactory. [e] Analysis for O and S satisfactory. [f] Analysis for S satisfactory. [g] Analysis of O and S satisfactory. [h] Analysis for O satisfactory.

Experimental Section[37]

Sulfonation of 5- and 7-Halogeno-8-quinolinols.—Halogeno-8-quinolinol (0.5 mol) (F, Cl, or Br) was dissolved in 300 ml of 20% oleum. The solution was heated to 170–180° with stirring. After the solution was allowed to cool to 40–50°, it was poured onto ice. The halogeno-8-quinolinolsulfonic acid was obtained by filtration, followed by washing with Me_2CO and drying at 70° overnight.

8-Quinolinol-7-sulfonic Acid (III).—A mixture of 5-chloro-8-quinolinol-7-sulfonic acid (IIb) (55 g, 0.2 mol), 4 g of Pd/C (10%) and 200 ml of H_2O containing 50 g of H_2SO_4 was shaken under 3 atm of H_2 in a Parr hydrogenator until 0.2 mol of H_2 was taken up. The mixture was heated to 80–90°, and the catalyst was removed by filtration. The warm solution was diluted with an equal volume of H_2O and refrigerated overnight. A yield of 29.5 g (60%) of product was obtained as the monohydrate by filtration, washing (Me_2CO), and drying at 70° overnight.

5-Iodo-8-quinolinol-7-sulfonic Acid (IVa).—8-Quinolinol-7-sul-

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(35) Infrared spectra will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

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(37) Methods found in the literature were used for the preparation of 7-chloro-8-quinolinol-5-sulfonic acid,[16] 7-bromo-8-quinolinol-5-sulfonic acid,[16] 7-nitro-8-quinolinol-5-sulfonic acid,[5] and 5-fluoro-8-quinolinol.[33] 8-Quinolinol-5-sulfonic acid, 7-iodo-8-quinolinol-5-sulfonic acid, 5-chloro-8-quinolinol, and 5-bromo-8-quinolinol were commercially available. Melting points were taken in a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 221 spectrophotometer. Gas chromatography was performed on a Varian Aerograph Model 1200 gas chromatograph with a flame ionization detector. Methods and columns were previously described.[16,39] Nmr spectra were taken with a Jeolco JMN-C-60HL spectrometer.

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TABLE II

PROTON CHEMICAL SHIFTS FOR 8-QUINOLINOLSULFONIC ACIDS[a] (TMS INTERNAL STANDARD)

Substituent on 8-quinolinol[b]	Proton 2	3	4	5	6	7
5-SO_3H	0.80 (q, J_{23} = 5, J_{24} = 1.5)	1.75 (q, J_{32} = 5, J_{34} = 9)	0.05 (q, J_{42} = 1.5, J_{43} = 9)		1.80 (d, J_{67} = 9)	2.58 (d, J_{76} = 9)
7-F, 5-SO_3H	0.82 (q, J_{23} = 5, J_{24} = 1.5)	1.88 (q, J_{32} = 5, J_{34} = 8)	0.23 (q, J_{42} = 1.5, J_{43} = 8)		1.90 (d, J_{HF} = 11)	
7-Cl, 5-SO_3H	0.89 (q, J_{23} = 5, J_{24} = 1.5)	1.93 (q, J_{32} = 5, J_{34} = 9)	0.44 (q, J_{42} = 1.5, J_{43} = 9)		1.93 (s)	
7-Br, 5-SO_3H	0.88 (q, J_{23} = 5, J_{24} = 1.5)	2.00 (q, J_{32} = 5, J_{34} = 9)	0.46 (q, J_{42} = 1.5, J_{43} = 9)		1.80 (s)	
7-I, 5-SO_3H	0.98 (q, J_{23} = 4, J_{24} = 1.5)	2.12 (q, J_{32} = 4, J_{34} = 9)	0.59 (q, J_{42} = 1.5, J_{43} = 9)		1.66 (s)	
7-NO_2, 5-SO_3H	0.85 (q, J_{23} = 5, J_{24} = 2)	1.94 (q, J_{32} = 5, J_{34} = 9)	0.54 (q, J_{42} = 2, J_{43} = 9)		1.43 (s)	
7-NH_2, 5-SO_3H	1.13 (d, J_{23} = 6)	2.30 (q, J_{32} = 6, J_{34} = 8)	0.40 (d, J_{43} = 8)		2.00 (s)	
7-SO_3H	0.73 (s)	1.70–1.95 (unresolved multiplet)	0.85 (s)	1.95 (d, J_{56} = 10)	2.19 (d, J_{65} = 10)	
5-F, 7-SO_3H	0.78 (q, J_{23} = 5, J_{24} = 1.5)	1.86 (q, J_{32} = 5, J_{34} = 9)	0.92 (q, J_{42} = 1.5, J_{43} = 9)		2.30 (d, J_{HF} = 9)	
5-Cl, 7-SO_3H	0.75 (d, J_{23} = 6)	1.79 (d, J_{32} = 6, J_{34} = 9)	0.84 (d, J_{43} = 9)		2.02 (s)	
5-Br, 7-SO_3H	0.74 (q, J_{23} = 5, J_{24} = 1.5)	1.78 (q, J_{32} = 5, J_{34} = 9)	0.92 (q, J_{42} = 1.5, J_{43} = 9)		1.86 (s)	
5-I, 7-SO_3H	0.80 (q, J_{23} = 5, J_{24} = 1.5)	1.87 (q, J_{32} = 5, J_{34} = 9)	1.10 (q, J_{42} = 1.5, J_{43} = 9)		1.62 (s)	
5-NO_2, 7-SO_3H	0.78 (q, J_{23} = 4, J_{24} = 1.5)	1.90 (q, J_{32} = 4, J_{34} = 9)	0.61 (q, J_{42} = 1.5, J_{43} = 9)		1.20 (s)	
5-NH_2, 7-SO_3H	0.89 (d, J_{23} = 6)	2.07 (q, J_{32} = 6, J_{34} = 9)	1.00 (s)		2.63 (s)	
5,7-$(SO_3H)_2$	0.73 (q, J_{23} = 6, J_{24} = 2)	1.68 (q, J_{32} = 6, J_{34} = 9)	0.09 (q, J_{42} = 1.5, J_{43} = 9)		1.60 (s)	

[a] Spectra were taken on 3% solutions of free base in DMSO-d_6; proton chemical shifts are given in parts per million (τ), J in hertz. [b] Registry numbers are, respectively, 84-88-8, 384-31-6, 3062-36-0, 3062-37-1, 547-91-1, 15851-63-5, 15851-62-4, 3062-35-9, 31568-78-2, 3244-71-1, 3062-38-2, 3075-21-6, 31568-82-8, 31568-83-9, 31568-84-0.

fonic acid (III) (2.24 g, 0.01 mol) and *N*-iodosuccinimide (2.25 g, 0.01 mol) were slurried in a mixture of 20 ml of MeOH and 5 ml of H_2O. Stirring was continued for 2 hr, and the product was removed by filtration. After washing with H_2O and Me_2CO and drying at 70° overnight, a yield of 89% of IVa was obtained. When ICl was employed for iodination, the iodosulfonic acid was obtained in 72% yield.

5-Nitro-8-quinolinol-7-sulfonic Acid (IVb).—A solution of 12g (0.053 mol) of III in 50 ml of H_2SO_4 was cooled to 0°, and 3.2 ml (0.051 mol) of HNO_3 was added dropwise with stirring. The temperature was maintained below 10°. Agitation was continued for 5 min, after completion of addition of the acid. The mixture was poured onto ice, and the product was recovered by filtration, followed by washing with H_2O and Me_2CO. A yield of 9.5 g (67%) of IVb was obtained.

5-Amino-8-quinolinol-7-sulfonic Acid (V).—A suspension of 6 g (0.022 mol) of IVb and 25 mg of PtO_2 in 50 ml of H_2O and 25 ml of DMF was heated to 70° and hydrogenated under 5 atm of H_2 in a Parr hydrogenator until 0.066 mol of H_2 was taken up. The amino derivative which was insoluble in the solvent mixture was removed along with the catalyst by filtration. The residue was extracted twice with a boiling mixture composed of 100 ml of DMF and 25 ml of H_2O. Upon cooling, 3.5 g (78%) of product was obtained.

7-Amino-8-quinolinol-5-sulfonic Acid.—A suspension of 8.1 g (0.03 mol) of 7-nitro-8-quinolinol-5-sulfonic-acid[5] and 50 mg of PtO_2 in 100 ml of 95% MeOH was shaken in a Parr hydrogenator until 0.09 mol of H_2 was consumed. The catalyst was removed by filtration, and the solvent was flash evaporated. The yield of product was 6.8 g (90%), as the hemihydrate, mp 292–293° dec.

8-Quinolinol-5,7-disulfonic Acid.—8-Quinolinol (29 g, 0.2 mol) was heated in 100 ml of 20% oleum to 150°, after which it was cooled and poured onto ice. The solution was diluted to 2000 ml, and 125 g (0.5 mol) of solid $CuSO_4 \cdot 5H_2O$ was added. After stirring overnight, 95 g of the Cu(II) salt of the disulfonic acid was obtained by filtration, followed by washing with Me_2CO and air drying. The salt was dissolved in 1500 ml of hot H_2O and treated with H_2S until all of the Cu(II) was precipitated as Cu_2S. The sulfide was removed by filtration, and the colorless filtrate was flash evaporated to near dryness. The residue was slurried in Me_2CO to remove all color, and 43 g of product was obtained after filtration. An additional crop of 4.3 g was recovered from the Me_2CO. The total yield of product was 85%, as the dihydrate, mp 310–315° dec.