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Preparation and Properties of 7-Formyl-8-hydroxy-5-quinolinesulfonic Acid

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8-Hydroxy-5-quinolinesulfonic acid (I), on condensation with formaldehyde in aqueous ammonia, produced 8-hydroxy-7-hydroxymethyl-5-quinolinesulfonic acid (IV), which, on oxidation with manganese (IV) oxide, gave 7-formyl-8-hydroxy-5-quinolinesulfonic acid (V). On treatment with boiling 6 M hydrochloric acid, V produced bis[α-hydroxy-(8-hydroxy-5-sulfo-7-quinolyl)methyl] ether (VIII).

It is known that 8-hydroxy-5-quinolinesulfonic acid (I), on condensation with formaldehyde and secondary amine, produces the corresponding Mannich base.[1] In the present study, it was found that 8-hydroxy-5-quinolinesulfonic acid (I), on heating at 90 °C for 3 h with formaldehyde in aqueous ammonia, afforded 8-hydroxy-7-hydroxymethyl-5-quinolinesulfonic acid (IV) in a 60% yield. In the course of our investigation, it was found that when this reaction was allowed to proceed at 90 °C for 40 min instead of 3 h, the major product was bis(8-hydroxy-5-sulfo-7-quinolylmethyl)amine (VII), admixed with a minute amount of IV, showing that the hydroxymethylation proceeded by way of the intermediate formation of the Mannich base (VII), which subsequently underwent hydrolysis on further heating at 90 °C. When the reaction of I with hexamethylenetetramine in aqueous ammonia was allowed to proceed at 90 °C for 3 h, a result similar to that of the formaldehyde–aqueous ammonia method was obtained.

On the other hand, when this reaction was allowed to proceed at 36 °C for 2 weeks, a mixture of IV and the Mannich base (VII), which was predominant, was formed. IV was converted to 7-formyl-8-hydroxy-5-quinolinesulfonic acid (V)[2] by oxidation with manganese(IV) oxide. The presence of a formyl group in V was confirmed by its infrared spectrum, which displayed two bands, at 2650 and 2800 cm^{-1}, indicating the characteristic carbon-hydrogen stretching frequency associated with the C–H of the formyl group. On the other hand, when a solution of I and formaldehyde in aqueous sodium hydroxide was heated at 90 °C for 3 h, contrary to our expectation of obtaining IV, 8,8′-dihydroxy-7,7′-methylenedi(5-quinolinesulfonic acid) (II) was produced in a 97% yield.

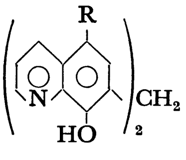
As was expected, on heating II with 50% sulfuric acid 7,7′-methylenedi(8-quinolinol) (III) was formed; on the same treatment IV also afforded III, the identity having been established by mixed mp and IR. The preparation of III by another route has already been reported by Ozawa and Shibuya.[3] The identity of the two compounds was proved by the mp and IR and mp of the diacetyl derivatives.

On heating V with 6 M hydrochloric acid at 100 °C for several minutes, a paste of well-defined crystal was formed in a good yield. This product was inferred to possess the (VIII) structure in consideration of its elemental composition and a mass-spectrometric examination.

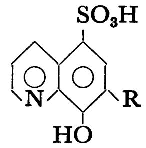
The PMR spectrum of VIII showed no –CH(OH)– signals, perhaps because of deuteration during the examination.

VIII would be formed upon the elimination of water between two molecules of the aldehyde hydrate. Such a dimerization is not unusual with formaldehyde or chloral. The tendency of V to form aldehyde anhydride (VIII) in a 6 M hydrochloric acid solution may be due to the fact that the electron-attracting character of sulfo group may favor the formation of a hydrate form.

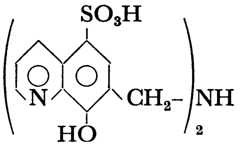
Mass Spectrometry. The characteristic features are that all the compounds examined underwent thermolyses prior to ionization. The mass-spectral data are listed in Table 1.



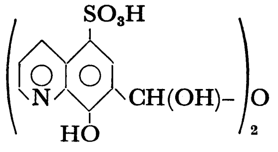
II R=SO_3H
III R=H



I R=H
IV R=CH_2OH
V R=CHO
VI R=CH=CH-COOH



VII



VIII

TABLE 1.

Compd	eV	°C	Peaks
II	75	230	302(100%), 298(15), 285(30), 283(38), 255(20), 158(83), 149(30), 145(88), 142(25), 136(18), 129(15), 117(25), 80(63), 64(158)
IV	70	210	302(100%), 298(9), 285(41), 283(26), 255(26), 158(81), 149(41), 145(70), 142(22), 136(19), 129(11), 117(22), 80(30), 64(63)
V	75	340	314(5%), 300(6), 299(30), 298(100), 270(40), 242(16), 241(16), 214(11), 188(13), 149(15), 135(24)
VII	70	230	327(3%), 312(6), 171(26), 170(94), 159(100), 158(69), 149(19), 145(36), 142(74), 130(84), 117(26), 115(36), 80(16), 64(96), 39(21)
VIII	75	180	336(28%), 261(22), 260(37), 259(67), 258(63), 232(13), 230(22), 195(76), 194(28), 193(59), 182(113), 178(81), 158(37), 152(37), 145(72), 143(100), 122(19), 117(85)

The relative intensities are given within parentheses. The mass spectra were recorded with a JEOL JMS-D100 mass spectrometer.

Experimental*

8,8′-Dihydroxy-7,7′-methylenedi(5-quinolinesulfonic Acid) (II). A solution of 5-sulfo-8-quinolinol dihydrate (10.44 g, 0.04 mol) and 36% formalin (30 g, 0.36 mol) in a 2.5 M sodium hydroxide solution (26 ml, 0.065 mol) was heated at 90 °C for 2 h. After cooling, the solution was acidified (T.B. 1.4) with hydrochloric acid; the crystals thus separated were filtered after the solution had stood for 2 days and then been dried at room temperature, yield, 9.3 g (97%) as monohydrate. Recrystallization from three hundred times its weight of boiling water yielded prismatic needles; mp 290—292 °C (foaming). It gives a dark green color with iron (III) chloride. IR (cm^{-1}, KBr), 3400 (–SO_3H), 3100 (–OH), 2950 (–CH_2–).

Found**: C, 47.44; H, 3.39; N, 5.76%. Calcd for $C_{19}H_{14}O_8N_2S_2 \cdot H_2O$: C, 47.50; H, 3.33; N, 5.83%.

Found: C, 48.72; H, 3.35; N, 5.77%. Calcd for $C_{19}H_{14}O_8N_2S_2 \cdot 0.5H_2O$: C, 48.41; H, 3.18; 5.94%.

8-Hydroxy-7-hydroxymethyl-5-quinolinesulfonic Acid (IV). **(A)** A solution of 5-sulfo-8-quinolinol dihydrate (10.44 g, 0.04 mol) and 36% formaldehyde (3.7 ml, 0.044 mol) in 7% aqueous ammonia (40 ml, 0.08 mol) was heated at 90 °C for 3 h and acidified (T.B. 1.4) while hot with 6 M hydrochloric acid; the crystals thus separated were filtered after the solution had stood for 4 days. The suspension of this crude product in 3 M hydrochloric acid (30 ml) was triturated at 90 °C for several minutes, filtered hot (filtrate F), washed with water and dried at 80 °C; yield, 6.12 g (60%). It forms as yellow thick plates (mp 289 °C(foaming)) and gives a deep green color with iron (III) chloride. For analysis, it was recrystallized from 300 times its weight of hot water. IR (cm^{-1}, KBr), 3450 (–CH_2OH), 3400 (–SO_3H), 3100 (–OH).

Found: C, 46.99; H, 3.36; N, 5.75%. Calcd for $C_{10}H_9O_5NS$: C, 47.06; H, 3.53; N, 5.49%.

Diacetyl Derivative of IV. This was made by heating a mixture of IV (260 mg), acetic anhydride (1 ml), and pyridine (1 ml) at 135 °C for 3 h, evaporating it *in vacuo* to dryness, acidifying with hydrochloric acid in cold, and washing with cold water; yield, 270 mg; mp 300 °C (foaming). It forms short needles.

Found***: C, 45.99; H, 3.97; N, 4.13%. Calcd for $C_{14}H_{13}O_7NS \cdot 1.5H_2O$: C, 45.90; H, 4.37; N, 3.83%.

Dibenzoyl Derivative of IV. A mixture of IV (260 mg), benzoyl chloride (420 mg), and pyridine (0.5 ml) was triturated at an ice-cold temperature for 0.5 h, allowed to stand at room temperature overnight, and then acidified (T.B. 1.8) with hydrochloric acid. The separated solid was filtered and treated with ethanol to give colorless prisms (300 mg), mp 288—290 °C (dec).

Found***: C, 57.58; H, 3.56; N, 3.35%. Calcd for $C_{24}H_{17}O_7NS \cdot 2H_2O$: C, 57.71; H, 4.21; N, 2.80%.

The filtrate, F, on concentration afforded fine needles (20 mg) mp 312 °C. It gives a dark violet color with iron(III) chloride and was identified as the Mannich base (VII) by IR.

(B) A solution of I dihydrate (5.22 g, 0.00 mol) and hexamethylenetetramine (0.51 g, 1/6 × 0.02 mol) in 7% aqueous ammonia (20 ml) was heated at 90 °C for 2 h. The further treatment was similar to that used for **(A)**. IV; yield, 2.92 g (57%); mp 289 °C (foaming). VII; yield, 50 mg; mp 312 °C. The two products were identified as IV and VII respectively by IR.

7,7′-Methylenedi(8-quinolinol) (III). A solution of II (200 mg) in 50% sulfuric acid (0.4 ml) was heated at 140 °C for one h. After cooling, on alkalifying with ammonia, the product was obtained as colorless, soft, thin plates; yield, 120 mg (86%).

On recrystallization from methanol, it formed compact prismatic needles; mp 185 °C; lit,[3] mp 170—180 °C, IR (cm^{-1}, KBr), 3100 (–OH), 2950, 1440 (–CH_2–).

Found: C, 75.26; H, 4.67; N, 9.04%. Calcd for $C_{19}H_{14}O_2N_2$: C, 75.50; H, 4.64; N, 9.27%.

Diacetyl Derivative of III. This crystallized as prisms from benzene; mp 170—172 °C; Lit,[3] mp 170—220 °C.

Found: C, 71.76; H, 4.81; N, 7.17%. Calcd for $C_{23}H_{17}O_4N_2$: C, 71.69; H, 4.42; N, 7.27%.

Monopicrate of III. This crystallized as rectangular thick plates from methanol; mp 245—246 °C (foaming).

Found: C, 56.30; H, 3.21; N, 12.88%. Calcd for $C_{19}H_{14}O_2N_2 \cdot C_6H_3O_7N_3$: C, 56.50; H, 3.20; N, 13.18%.

A solution of IV (500 mg) in 50% soufuric acid (1 ml) was heated at 140—145 °C for 2.5 h. On further working, the product (310 mg) was obtained as prisms (mp 185 °C) and identified as III by a mixed mp and by IR.

Bis(8-hydroxy-5-sulfo-7-quinolylmethyl)amine (VII). **(A)** On heating a mixture of I dihydrate (5.22 g, 0.02 mol), hexamethylenetetramine (0.51 g, 1/6 × 0.022 mol), and 7% aqueous ammonia (20 ml) at 80 °C for a few minutes, a clear solution was obtained. It was allowed to stand at 36 °C for 2 weeks. When the reaction mixture was then acidified (T.B. 1.4) with hydrochloric acid, soft precipitates with a gelatinous appearance were separated. The precipitates were filtered with suction, washed with water, and dried at 80 °C; yield, 3.76 g. On recrystallization from one thousand times its weight of boiling water, 2.17 g. (44.2%) of fine needles (mp 312 °C) were obtained. VII gives a dark violet color with iron (III) chloride. IR (cm^{-1}, KBr), 3400 (–SO_3H), 3200, 2850 (O–H), 1540, 1140 (–CH_2–NH–CH_2–).

Found: C, 48.52; H, 3.53; N, 8.38%. Calcd for $C_{20}H_{17}O_8N_3S_2$: C, 48.88; H, 3.46; N, 8.55%.

From the filtrate of the recrystallization, thick plates (1.16 g) were isolated on concentrating. They were after further recrystallization, identified as IV by IR and mp.

(B) A solution of I dihydrate (10.44 g, 0.04 mol) and 36% formalin (3.7 g, 0.044 mol) in 7% aqueous ammonia (40 ml, 0.08 mol) was heated at 90 °C for 40 min and acidified (T.B. 1.4) with 6 M hydrochloric acid; a yellow gelatinous solid thus separated was filtered after standing overnight in a refrigerator, washed well with water, and dried on a plate; yield, 5.9 g.

A portion of it, on recrystallization from hot water, yielded fine yellow needles; mp 312 °C. It gives a dark violet color with iron (III) chloride and was identified as VII by IR and mp.

7-Formyl-8-hydroxy-5-quinolinesulfonic Acid (V). To a hot solution of IV (4.1 g, 0.016 mol) and sodium acetate hydrate (2.2 g, 0.016 mol) in water (300 ml), commercial manganese dioxide (16 g) was added; the mixture was then heated at 95 °C for 2 h with vigorous stirring and filtered hot (charcoal). From the filtrate, the product was obtained as colorless thin plates on concentrating up to 150 ml, acidifying (T.B. 1.4) with hydrochloric acid, and standing overnight. It was recrystallized from fifty times its weight of hot water; yield,

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* All the elemental analyses, unless stated otherwise, were performed after the material had been dried at 120 °C *in vacuo* over P_2O_5.

** Dried at room temperature over potassium hydroxide *in vacuo.*

*** Vacuum-dried at room temperature over potassium hydroxide.

1.96 g (48.2%). It turned to a black solid at 317 °C with preliminary darkening. It gives no color† reaction with iron(III) chloride; however, the mixture gradually developed a light green color after standing for 3 h at room temperature. IR (cm^{-1}, KBr), 2400 (-SO_3H), 3100 (OH), 2800, 2650 (H-CO-), 1740 (HC-O).

Found***: H_2O, 12.41; C, 41.63; H, 3.69; N, 5.06%. Calcd for $C_{10}H_7O_5NS \cdot 2H_2O$: H_2O, 12.46; C, 41.52; H, 3.81; N, 4.84%. Found: C, 47.20; H, 2.95; N, 5.76%. Calcd for $C_{10}H_7O_5NS$: C, 47.43; H, 2.77; N, 5.53%.

Mono-sodium salt of V. This was crystallized from water as colorless, soft, fine needles.

Found: C, 43.53; H, 2.66; N, 5.29%. Calcd for $C_{10}H_6O_5NSNa$: C, 43.64; H, 2.18; N, 5.09%.

3-(8-Hydroxy-5-sulfo-7-quinolyl)acrylic Acid (VI). A solution of V (0.5 g, 0.002 mol), malonic acid (0.32 g, 0.003 mol), and potassium hydroxide (0.5 g) in water (8 ml) was heated at 80 °C for 12 h and then at 95 °C for 5 h, thereafter it was acidified with hydrochloric acid; yield, 0.3 g (51%). Recrystallization from 300 times its weight of hot water afforded glistening thick plates; mp 287 °C (with foaming). VI gives a deep green color with iron(III) chloride.

Found***: C, 47.01; H, 3.36; N, 4.54%. Calcd for $C_{12}H_9O_6NS \cdot 0.5H_2O$: C, 47.37; H, 3.29; N, 4.64%.

Bis[α-hydroxy-(8-hydroxy-5-sulfo-7-quinolyl)methyl] Ether (VIII). A mixture of V dihydrate (1.16 g, 0.004 mol) and 6 M hydrochloric acid (8 ml), on heating with stirring at 100 °C, soon turned to a clear solution; it began to become turbid after 6 min and became a crystal paste after 10 min further heating.

It was diluted with water (8 ml), filtered after standing in a refrigerator overnight, washed with water, and dried at room temperature; yield, 0.96 g (80%).

Recrystallization from 55 times its weight of hot water, with the addition of a small amount of 3 M hydrochloric acid, afforded stout prismatic needles; mp 250—255 °C (foaming). VIII gives a deep green color with iron(III) chloride. It is unaltered when the solution in 1% sodium hydroxide is heated over free flame for a few min.

^{1}H NMR (Me_2SO-d_6): H-3: δ 7.95 (2H, dd, $J_{3,2}=5.0$; $J_{3,4}=9.0$), H-6: δ 8.00 (2H, s), H-2: δ 9.05 (2H, dd, $J_{2,3}=5.0$; $J_{2,4}=1.5$), H-4: δ 9.52 (2H, dd, $J_{4,2}=1.5$; $J_{4,3}=9.0$). IR (cm^{-1}, KBr), 3420, 2500 (O-H), 1180 (C-O-C).

Found***: C, 39.67; H, 3.48; N, 4.93%. Calcd for $C_{20}H_{16}O_{11}N_2S_2 \cdot 4H_2O$: C, 40.26; H, 4.03; N, 4.70%.

Found: C, 42.18; H, 2.87; N, 5.16%. Calcd for $C_{20}H_{16}O_{11}N_2S_2 \cdot 2H_2O$: C, 42.86; H, 3.57; N, 5.00%.

Tetraacetyl Derivative of VIII. A mixture of VIII (200 mg), acetic anhydride (2 ml), and concentrated sulfuric acid (one drop) was heated at 130 °C for 3 h and evaporated *in vacuo*, and the residue was treated with ice. The thick plates were filtered, washed with cold water, and dried *in vacuo* at room temperature; mp 263 °C (dec).

Found: C, 46.27; H, 3.11; N, 3.46%. Calcd for $C_{28}H_{24}O_{15}N_2S_2 \cdot 2H_2O$: C, 46.15; H, 3.85; N, 3.85%.

We wish to thank Dr. Yoshio Matsumoto for generously allowing one of us (K.M.) to complete this work in his laboratory and Dr. Chiji Yamazaki for his helpful interpretation of the physical data and for the NMR spectral measurements.

References

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2) Fiedler reported the formation of V through another route of preparation, but without any characterization of this compound H. Fiedler, *Archiv. Pharmaz.*, **297**, 108 (1964). To our knowledge, II, IV, VII, and VIII have not heretofore been reported.

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† A very concentrated solution gives a faint brownish yellow color.