[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF LOUISVILLE]

2-, 3- and 4-Methyl Substituted 8-Quinolinols

BY J. P. PHILLIPS

With the investigation of 3-methyl and 2,3-dimethyl-8-quinolinol here reported all seven 8-quinolinols containing methyl groups in the pyridine ring have been made and their chelating properties studied. The relations between the properties of these compounds and their formation of chelates is discussed.

The discovery that 2-substituted 8-quinolinols do not form insoluble chelates with aluminum under conditions where 8-quinolinol quantitatively precipitates aluminum[1] has led to an investigation of possible reasons for this increased selectivity.[2,3] Since the most usual explanation is steric hindrance to chelate formation by the 2-substituent, it is desirable to investigate the chelating behavior of isomers containing the same substituent in other positions of the ring. From the standpoint of chemical activity a methyl group is the simplest substituent. Most of the possible 8-quinolinols with methyl groups in the pyridine ring have already been studied, and the series is now completed with the preparation of 3-methyl and 2,3-dimethyl-8-quinolinol.

It has been noted previously that substituents in the benzene ring of 8-quinolinol have little steric effect, if any, on chelate formation.[4,2]

Experimental

Preparation of 3-Methyl-8-quinolinol.—In a three-necked flask equipped with stirrer, condenser and dropping funnel is placed 36.5 g. (0.25 mole) of *o*-aminophenol hydrochloride, 10 g. of arsenic pentoxide and 75 ml. of concentrated hydrochloric acid. The mixture is heated quickly to 100–120° and 20.0 g. (0.29 mole) of methacrolein added rapidly through the dropping funnel. A mild reaction occurs which is finished after about five minutes. The mixture is steam distilled briefly to remove volatile impurities and then neutralized with sodium hydroxide solution. On steam distillation the product comes over in the form of white crystals which become slightly reddish on standing; yield 1.5 g. (4%). After two crystallizations from dilute ethanol white bladed crystals showing parallel extinction under a polarizing microscope are obtained; m.p. 112–113°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.44; H, 5.70; N, 8.80. Found: C, 74.9; H, 5.63; N, 8.93.

Properties.—Quantitative dibromination with standard potassium bromate according to the method used for determining 8-quinolinol[5] indicated a purity of 99.6 ± 0.3% (3 trials).

The ultraviolet absorption spectra in 0.1 *N* sodium hydroxide and hydrochloric acid were determined from 220–400 mμ using a Beckman model DU quartz spectrophotometer with 1.00-cm. cells. Beer's law was obeyed over the concentration range used. The acid and base ionization constants were measured by the spectrophotometric method previously described,[6] using twenty 0.004% solutions of 3-methyl-8-quinolinol ranging in *p*H from 2–12, *p*H adjustment being made by additions of small amounts of dilute hydrochloric acid or sodium hydroxide. The ionic strengths of the solutions were about 0.1, the temperature of measurement was room temperature, 25 ± 3°. The results were graphed and calculated at both 280 and 340 mμ. The approximate solubility in water at about 30° was determined by pipetting 5.00 ml. of the saturated solution into a 25-ml. volumetric flask, diluting to the mark with 0.1 *N* hydrochloric acid. Comparison of the extinction of this solution at 310 and 330 mμ with that of weighed amounts of the compound dissolved in 0.1 *N* acid gave the solubility.

Sulfonating with fuming sulfuric acid by the Matsumura procedure[7] gave apparently the 5-sulfonic acid derivative, a compound forming nearly colorless, fluorescent needles when crystallized from water and giving a green color with ferric iron.

3-Methyl-8-quinolinol forms insoluble chelates with aluminum, cupric, zinc and ferric ions in acetate buffers of *p*H 5.8, and also with magnesium ion in alkaline solution.

Preparation of 2,3-Dimethyl-8-quinolinol.—This compound was made by the same procedure described for 3-methyl-8-quinolinol substituting 25 g. of tiglaldehyde for the methacrolein; yield 2 g. (5%). After two crystallizations from dilute ethanol clear rhomboid crystals having symmetrical extinction under a polarizing microscope were obtained; m.p. 94–95°.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.41; N, 8.09. Found: C, 76.1; H, 6.49; N, 8.26.

Properties.—Quantitative dibromination with standard bromate indicated a purity of 99.8%. The 5,7-dibromo derivative precipitated under the conditions of the analysis was filtered off and recrystallized from alcohol as fine white needles, m.p. 151–152°.

Analysis of the magnesium chelate of 2,3-dimethyl-8-quinolinol by ignition to magnesium oxide gave 5.7% Mg; calculated for $Mg(C_{11}H_{10}NO)_2 \cdot 2H_2O$: 6.0%.

The ultraviolet absorption spectra in acid and base from 220–400 mμ were determined, the ionization constants measured on twenty 0.004% solutions at 270, 280 and 340 mμ, and the approximate water solubility at 30° calculated by the same methods used with 3-methyl-8-quinolinol.

Sulfonation with fuming sulfuric acid gave apparently 2,3-dimethyl-8-quinolinol-5-sulfonic acid, yellow needles having parallel extinction. The ultraviolet spectrum of this compound in 0.1 *N* sodium hydroxide showed absorption maxima at 258 and 348–350 mμ. Coupling with diazotized *p*-toluidine gave an orange-red dye; coupling of 2,3-dimethyl-8-quinolinol with diazotized *p*-toluidine gave a red-brown dye.

2,3-Dimethyl-8-quinolinol forms insoluble chelates with Fe^{+3}, Cu^{+2}, Zn^{+2}, Co^{+2}, Ni^{+2}, Cd^{+2}, UO_2^{+2}, Hg^{+2}, Pb^{+2}, ZrO^{+2}, Ag^{+1} and Bi^{+3} in acetate buffers of *p*H 5.8. It did not form an insoluble chelate with aluminum under these conditions. Sensitivity tests by the method of Irving, Butler and Ring[2] gave as the minimum detectable amount of copper in buffers of *p*H 5.8 and 8.4 about 2 γ/ml.; the minimum zinc detectable at *p*H 5.8 was about 3 γ/ml.

Discussion

The order of increasing basicity (and decreasing acidity) expected for the methyl substituted 8-quinolinols on the basis of the electron releasing tendencies of methyl groups would be

$$3\text{-}CH_3 < 4\text{-}CH_3 < 2\text{-}CH_3 < 3,4\text{-}(CH_3)_2 < 2,3\text{-}(CH_3)_2 < 2,4\text{-}(CH_3)_2$$

With the exception of the slightly anomalous position of 8-hydroxyquinaldine this is the order observed (Table I). An attempt to relate the base strengths of the compounds with the *p*H at which their metal chelates precipitate has shown[3] that although the more basic compounds seem to precipitate metals at slightly higher *p*H values, the differences are not significant enough to have practical application. The only selectivity encountered

(1) Merritt and Walker, *Anal. Chem.*, **16**, 387 (1944).
(2) Irving, Butler and Ring, *J. Chem. Soc.*, 1489 (1949).
(3) Phillips and Merritt, THIS JOURNAL, **71**, 3984 (1949).
(4) Phillips and Price, *ibid.*, **73**, 1875 (1951).
(5) Smith, *Analyst*, **64**, 577 (1939).
(6) Phillips and Merritt, THIS JOURNAL, **70**, 410 (1948).
(7) Matsumura, *ibid.*, **49**, 813 (1927).

in the methyl substituted 8-quinolinols is the failure of 2-methyl, 2,3-dimethyl, 2,4-dimethyl and 2,3,4-trimethyl-8-quinolinol to precipitate aluminum.

TABLE I

ACIDIC AND BASIC IONIZATION CONSTANTS OF 8-QUINOLINOLS

Substituent	$K_b \times 10^{10}$	$K_a \times 10^{10}$
None[1]	8.32	1.95
3-CH_3	8.71	1.78
2-CH_3[6]	35.5	0.490
4-CH_3[6]	36.4	1.00
3,4-$(CH_3)_2$[6]	63.1	0.892
2,3-$(CH_3)_2$	74.1	.630
2,4-$(CH_3)_2$[6]	159	.252

The ultraviolet absorption spectra of these compounds in acid and base are very similar to 8-quinolinol[8,9] (Table II). The longest wave length of maximum absorption in both acid and base is shortened by the presence of a 2-methyl group and the molecular extinction at this band is highest for the compounds containing a 4-methyl group.

TABLE II

ABSORPTION MAXIMA IN ULTRAVIOLET SPECTRA OF METHYL-8-QUINOLINOLS[a]

Substituent	mμ	mμ	mμ
	A, in 0.1 *N* hydrochloric acid		
2-CH_3[1]	255(44000)	320(3100)	345(1700)
3-CH_3	254(45000)	320(2300)	355(1900)
4-CH_3[1]	250(44000)	315–318(1700)	350–353(2400)
2,3-$(CH_3)_2$	255(45000)	323(3700)	342(1900)
2,4-$(CH_3)_2$[1]	252(48000)	318(3100)	342(2400)
3,4-$(CH_3)_2$	252(40000)	318(2100)	353(2500)
2,3,4-$(CH_3)_3$	255(44000)	316(2500)	346–349(2600)
	B, in 0.1 *N* sodium hydroxide		
2-CH_3[1]	255(30000)		335(3000)
3-CH_3	256–257(30000)		355(2700)
4-CH_3[1]	253(28000)		343(3900)
2,3-$(CH_3)_2$	257(37000)		335(3300)
2,4-$(CH_3)_2$[1]	255(31000)		337(4200)
3,4-$(CH_3)_2$	255(35000)		350–353(3800)
2,3,4-$(CH_3)_3$	255(41000)		340–345(4200)

[a] Figures in parentheses are molecular extinctions.

The solubilities of the methyl-8-quinolinols are with the exception of 8-hydroxyquinaldine very low: for example, a saturated solution of 3-methyl-8-quinolinol has a molarity of 5.4×10^{-4}, of 2,3-dimethyl-8-quinolinol a molarity of 4.8×10^{-4}, as compared to 2.67×10^{-3} for 8-hydroxyquinaldine.

Attempts to correlate various properties of methyl substituted 8-quinolinols with their formation of metal chelates led to the following generalizations: (1) The presence of a group in the 2-position is sufficient to prevent aluminum from forming an insoluble chelate.[2,3] (2) The lower the *p*H at which a metal is precipitated the more insoluble the metal chelate is; this is the same relation observed in the precipitation of metals as hydroxides by ammonia.[10] (3) There appears to be no simple relation between ionic radii of metals and their conditions of chelate formation with 8-quinolinols. (4) The more basic (and less acidic) substituted 8-quinolinols precipitate metal chelates at higher *p*H values.[3]

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(8) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).
(9) Phillips, Huber, Chung and Merritt, *ibid.*, **73**, 630 (1951).
(10) Phillips and Price, *ibid.*, **73**, 4414 (1951).

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NOTES

Manometric Estimation of Citric Acid

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A number of methods, enzymatic and chemical, have been described for the determination of small amounts of citric acid. Of the chemical methods, the majority involve the conversion of citric acid to pentabromoacetone, which may be estimated by various gravimetric, titrimetric or colorimetric procedures. The recent modifications[1-3] of this method have simplified it and increased the sensitivity. However, even in the simplified methods, the procedures are quite laborious. The method described in this communication is considerably faster and simpler to carry out.

Citric acid (14–400 micrograms) is oxidized manometrically under controlled conditions with ceric sulfate; the CO_2 produced is a measure of citric acid concentration.

Procedure

Manometric Estimation of Citric Acid.—Warburg flasks of about 20-ml. capacity with or without a center well and a side-arm of 1-ml. capacity are usually employed. The citric acid solution, usually 1 ml., is added to the main compartment. 0.5 ml. of 6 *N* H_2SO_4 is next pipetted into the main compartment to liberate all of the bound CO_2. 0.4 ml. of saturated ceric sulfate (a saturated solution is prepared by heating on a steam-bath an excess of the compound in 4 *N* H_2SO_4 for 6 to 12 hours with occasional stirring) is added to the side-arm. The control vessel is made up in the same way, excepting that 1 ml. of distilled water is placed in the main compartment, in place of the citric acid solution. The bath temperature is adjusted to 30°. After a 10-minute shaking period with the stopcocks open for equilibration, the manometric fluid is adjusted so as to provide a maximum scale for reading and the stopcocks are closed. If equilibration is attained, the content of the side-arm is delivered into the main compartment and the manometers quickly replaced on the bath. Readings are then taken every two or three minutes until the delta values (CO_2 evolution per unit time) of the control and the experimental manometers are equal on two successive readings. The reaction is usually complete in less than 10 minutes.

(1) H. H. Taussky and E. Shorr, *J. Biol. Chem.*, **169**, 103 (1947).
(2) S. Natelson, J. K. Luguvoy and J. B. Pincus, *ibid.*, **170**, 597 (1947).
(3) G. H. Wolcott and P. D. Boyer, *ibid.*, **172**, 729 (1948).