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The Mercuration of 8-Hydroxyquinoline and Some of Its Metal Chelates[1]

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Received April 11, 1969

The mercuration of 8-hydroxyquinoline (oxine) and some of its metal chelates has been studied. The mercurated chelates were decomposed in hydrochloric acid-*d* to furnish the deuterated ligand which was analyzed by nuclear magnetic resonance spectroscopy to determine the sites of substitution. Chemical shifts for the phenol-ring protons in oxine were assigned by analogy to the 5-acetyl derivative. Treated with an excess of mercurating reagent, the oxine chelates gave 5,7-dimercurated derivatives. No evidence for serious steric hindrance to substitution in the 7 position was obtained, even in tris chelates. A mixture of 5- and 7-monosubstituted derivatives was obtained when the ligand concentration greatly exceeded that of the mercurating agent. Substitution in the pyridine ring of the oxine ligand did not occur.

Introduction

Conflicting reports concerning the nature of the products of the ring substitution reaction (mercuration) of 8-hydroxyquinoline with mercury(II) salts are found in the literature.[2-6] It has been stated, *a priori*, that the reaction of an equimolar amount of mercury(II) acetate with 8-hydroxyquinoline in glacial acetic acid gives exclusively 5-acetoxymercury(II)-8-hydroxyquinoline.[2,3] With the mercurating reagent taken in excess, the 5,7-dimercurated derivative was claimed.[3] A proof of the structure of these products has not appeared.

The present work was undertaken to determine the sites of substitution and to extend the study to the mercuration of metal chelates of the ligand. It was of special interest to determine whether the 7 position in the ligand ring is sterically available for substitution in octahedral complexes. It was also of interest to determine whether the normally inert pyridine ring of the ligand is more labile to substitution in the metal chelates than in the free ligand.

Experimental Section

Materials.—Common chemicals were of reagent grade quality. Commercial 8-hydroxyquinoline (Aldrich Chemical Co.) was purified by recrystallization from aqueous ethanol and sublimation *in vacuo*. Deuterium oxide, of stated isotopic purity of 99.5%, was used as obtained from General Dynamics Corp.

The metal derivatives of 8-hydroxyquinoline were prepared by accepted procedures.[7-9] The analytical data follow where OX = C_9H_6NO. *Anal.* Calcd for $Cu(OX)_2 \cdot 2H_2O$: C, 55.7; H, 4.12; N, 7.23. Found: C, 55.1; H, 3.28; N, 7.18. Calcd for $Pb(OX)_2$: C, 43.7; H, 2.42; N, 5.65. Found: C, 42.2; H, 2.50; N, 5.99. Calcd for $Cr(OX)_3$: C, 67.0; H, 3.87; N, 8.87. Found: C, 67.1; H, 3.69; N, 8.87. Calcd for $Co(OX)_3$: C, 66.0; H, 3.67; N, 8.56. Found: C, 66.5; H, 3.97; N, 8.82.

The 5-acetyl-8-hydroxyquinoline was prepared by the method of Matsumura.[10] The chromium(III) chelate of the 5-acetyl derivative was prepared as above for the 8-hydroxyquinolinate. *Anal.* Calcd for $CrC_{33}H_{24}N_3O_6$: C, 64.8; H, 3.93; N, 6.85. Found: C, 61.8; H, 3.94; N, 6.71.

Mercuration Reactions.—The desired amount of mercury(II) oxide, dissolved in glacial acetic acid, was added to a solution of 8-hydroxyquinoline or a metal chelate in the same solvent and allowed to stand. The acetoxymercury derivatives precipitated over periods varying from several hours to a few days. In some cases it was found preferable to convert to bromomercury derivatives with potassium bromide. Because the solids obtained were insoluble in all common solvents, purification was limited to thorough washing with acetic acid, water, ethanol, and ethyl ether in that order.

Ligand Recovery.—A quantity of mercurated chelate was decomposed at 70° in a solution of hydrochloric acid-*d* prepared by the dissolution of freshly distilled (from quinoline) acetyl chloride in deuterium oxide. Solid thioacetamide was added to precipitate mercury(II) sulfide which was removed by filtration. The neutralized filtrate (NaOH) was extracted with ethyl ether to separate the deutrated ligand which was isolated by evaporation of the ether and purified by vacuum sublimation. A sample of 8-hydroxyquinoline carried through this procedure did not suffer exchange of deuterium for the ring hydrogen atoms.

Chemical Analyses.—The C, H, and N analyses were obtained with an F & M carbon–hydrogen–nitrogen analyzer, Model 185. Satisfactory results were obtained with the pure chelates and the mercurated copper chelate. The other mercurated products gave erratic results. Mercury analyses, done as a gravimetric HgS procedure, were consistently good. Copper was determined as the sulfide, and cobalt as the $CoCl_4^{2-}$ complex by the spectrophotometric procedure of Schmidt and Taube.[11] Where quoted, oxygen was obtained by difference.

Nuclear Magnetic Resonance Spectroscopy.—Spectra were recorded on a Varian Model A-60 spectrometer using tetramethylsilane as the internal reference standard. Carbon tetrachloride or chloroform-*d* were used as solvents.

Results and Discussion

The conditions and the products of the mercuration reactions are described in Table I. Formulas of products in agreement with the analytical data are given in the last column. Treated with a fivefold excess of mercurating agent, 8-hydroxyquinoline was converted to the mercury(II) chelate of the dimercurated ligand, I. A monomercurated product, II, was obtained when an insufficient amount of mercurating agent was used. The same product, II, was obtained from the mercuration of the lead(II) chelate which was the only chelate

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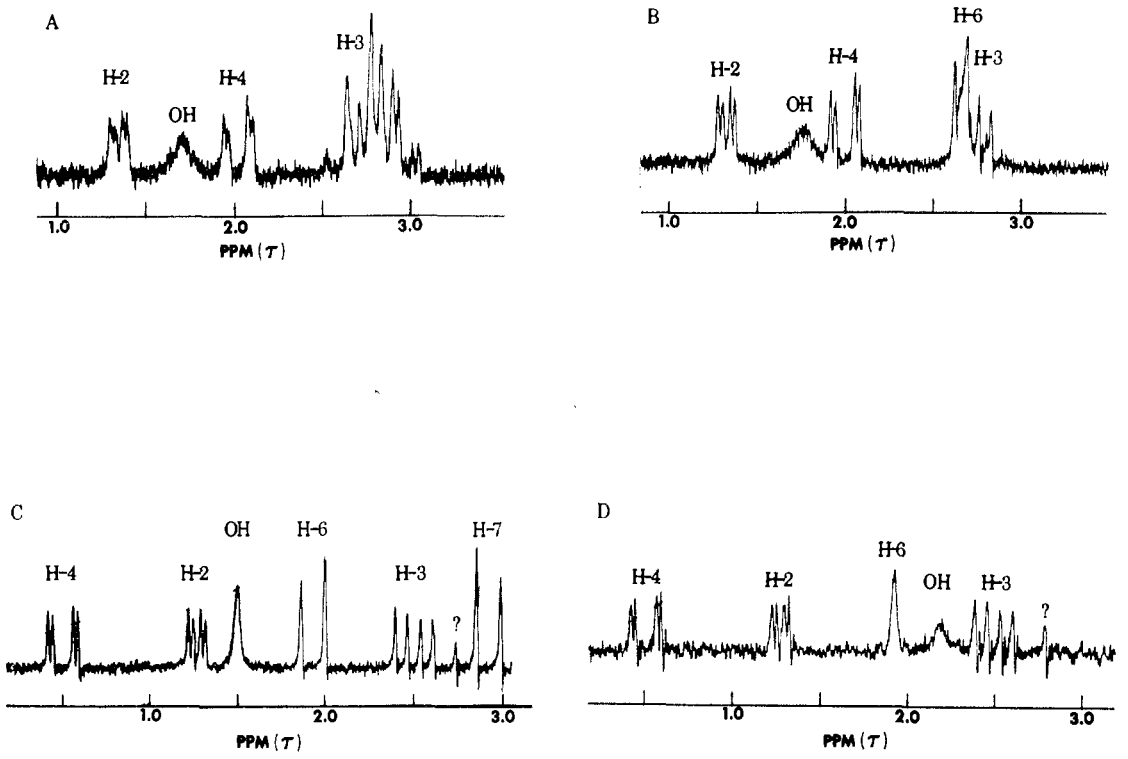

Figure 1.—Nmr spectra of 8-hydroxyquinoline derivatives: A, 8-hydroxyquinoline, B, 8-hydroxyquinoline-$d_{5,7}$; C, 5-acetyl-8-hydroxyquinoline; D, 5-acetyl-8-hydroxyquinoline-d_7. (Spurious signal marked ? in C and D is probably due to chloroform.)

TABLE I

MERCURATION PRODUCTS FROM 8-HYDROXYQUINOLINE AND SOME METAL CHELATES

Substrate[a]	Amt of substrate used, mmol	Amt of HgO, mmol	Hg anal., % Calcd	Hg anal., % Obsd	Product no.	Apparent formula
HOX	10.0	50.0	62.8	62.9	I	$Hg(C_9H_4NO(HgBr)_2)_2$
HOX	50.0	10.0	49.8	50.7	II	$C_9H_5NOH(HgC_2H_3O_2)$
$Pb(OX)_2$	10.0	10.0	49.8	49.5	II	$C_9H_5NOH(HgC_2H_3O_2)$
$Cu(OX)_2 \cdot 2H_2O$	12.8	12.8	46.2	47.3	III	$Cu(C_9H_5NO(HgC_2H_3O_2))_2$[b]
$Cu(OX)_2 \cdot 2H_2O$	1.20	15.0	57.9	57.0	IV	$Cu(C_9H_4NO(HgC_2H_3O_2)_2)_2$[c]
$Co(OX)_3$	4.30	80.0	55.5	55.2	V	$Co(C_9H_4NO(HgBr)_2)_3$[d]
$Cr(OX)_2$	2.24	50.7	55.9	56.2	VI	$Cr(C_9H_4NO(HgBr)_2)_3$
$Cr(5\text{-}OAcOX)_3$	0.33	7.60	...	...	VII	$Cr(C_{11}H_7NO_2HgBr)_3$[e]

[a] HOX = C_9H_6NOH; OX = C_9H_6NO; 5-OAcOX = $C_{11}H_8NO_2$. [b] *Anal.* Calcd: C, 30.4; H, 1.84; N, 3.22; O, 11.0; Cu, 7.32; Hg, 46.2. Found: C, 28.8; H, 1.79; N, 3.28; O, 12.1; Cu, 6.70; Hg, 47.3. [c] *Anal.* Calcd: C, 22.5; H, 1.44; N, 2.02; O, 11.5; Cu, 4.58; Hg, 57.9. Found: C, 22.4; H, 1.66; N, 2.19; O, 12.4; Cu ,4.45; Hg, 57.0. [d] *Anal.* Calcd: Co, 2.66. Found: Co, 2.31. [e] *Anal.* Calcd: C, 27.4; H, 1.45; N, 2.90. Found: C, 22.1; H, 1.27; N, 2.22.

that could not be recovered as the intact mercurated complex. Both monomercurated, III, and dimercurated, IV, ligands were obtained from the copper chelates in agreement with the observations of Chawla and Jones.[12] The cobalt(III) and chromium(III) chelates were treated with an excess of mercurating agent to force the substitution beyond the monomercurated stage. Products V and VI, both containing dimercurated ligands, were obtained. The chelate tris(5-acetyl-8-hydroxyquinolinato)chromium(III) furnished an impure product, VII, which consisted mainly of the tris chelate containing three monomercurated ligands.

The mercurated products were further characterized by decomposition in hydrochloric acid-*d*. Warm dilute mineral acids cleave the carbon–mercury bonds and, if the deuterated acid is used, replace the mercury by deuterium atoms.[13] At the same time, the chelated ligands are freed from the metal ion and converted to the acid form. The determination of the positions of the deuterium atoms in the free ligands by nmr spectroscopy allowed the assignment of the mercuration sites.

Figure 1 shows the nmr spectra from which the data in Table II were obtained. The numbering system used appears in Figure 2. The three protons in the pyridine ring of 8-hydroxyquinoline exhibit an ABX spectrum (A, Figure 1) with the quartet appearing farthest downfield, centered at τ 1.33, assigned to the H-2 proton. The quartet centered at τ 2.02 has been assigned to H-4 while the absorption by H-3 is assigned to the quartet at still higher fields, centered at τ 2.68,

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TABLE II
NMR SPECTRAL DATA FOR 8-HYDROXYQUINOLINE DERIVATIVES

	Chemical shifts, τ						Coupling constants, cps			
	H-2	H-3	H-4	H-5	H-6	H-7	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{6,7}$
HOX[a]	1.33	2.68	2.02	*b*	*b*	*b*	4.4	1.7	8.3	...
HOX-$d_{5,7}$	1.33	2.75	2.00	...	2.65	...	4.2	1.8	8.4	...
5-OAc–HOX	1.25	2.50	0.50	...	1.95	2.92	4.0	1.4	8.4	8.0
5-OAc–HOX-d_7	1.25	2.48	0.49	...	1.89	...	4.0	1.6	8.4	...

[a] HOX = C_9H_6NOH; 5-OAc–HOX = $C_{11}H_9NO_2$. [b] Unresolved multiplets.

overlapping the spectrum of the phenol-ring protons. These results as well as the J values given in Table II agree precisely with already published data.[14]

The deuterated 8-hydroxyquinoline (HOX-$d_{5,7}$) obtained from bis(dibromomercury(III)-8-hydroxyquinolinato)mercury(II) gave a simplified spectrum (B, Figure 1). The ABX system for the pyridine-ring protons was clearly identified through chemical shift and coupling constant data. Assignments of the H-2, H-3, and H-4 chemical shifts appear in Table II. The phenol-ring multiplets in the spectrum of the parent molecule disappeared in the spectrum of the deuterated analog leaving a slightly broadened singlet at τ 2.65. Therefore, a single proton remained on the phenol ring in agreement with the integrated proton count of five for the whole molecule. The spectra of HOX-$d_{5,7}$ obtained from the mercuration products IV, V, and VI gave the same nmr pattern. The assignment of H-6 to the singlet at τ 2.65 is based on the results obtained from the experiments with the 5-acetyl derivatives described below.

A comparison of the coupling constants in Table II for the pyridine-ring protons of the 5-acetyl derivative and the parent molecule allow the assignment of the quartets centered at τ 1.25 and τ 2.50 to H-2 and H-3, respectively. The H-4 signal is shifted from τ 2.02 in oxine to τ 0.50 in the 5-acetyl compound. This is a consequence of the strong deshielding effect of the adjacent carbonyl function of the 5-acetyl group.[15] The spectrum of the phenol-ring protons (C, Figure 1) is an AB system with coupling constant $J_{6,7}$ of 8.0 cps. The lower field doublet centered at τ 1.95 is assigned to H-6 because of its proximity to the acetyl group.[15] The doublet at τ 2.92 is, therefore, the H-7 signal. A broad resonance appeared at τ 1.50 which was assigned to the phenolic proton because its chemical shift varied with concentration.

The mercuration of the 5-acetyl-substituted tris chelate of chromium(III) gave product VII which was converted to the deuterated ligand as before. The recovered ligand, 5-acetyl-8-hydroxyquinoline-d_7, gave an nmr spectrum (D, Figure 1) in which the doublet at τ 2.92 was no longer observable and the doublet at τ 1.95 had collapsed into a broadened singlet at τ 1.89. Obviously, the substitution of mercury into the 5-acetyl-substituted chelate ring took place at position 7. Thus, because both the 5 and 7 positions are shown to be available for substitution in chelated molecules, we conclude that all of the dimercurated tris chelates of 8-hydroxyquinoline were substituted at positions 5 and 7. The proposed structures are shown in Figure 2.

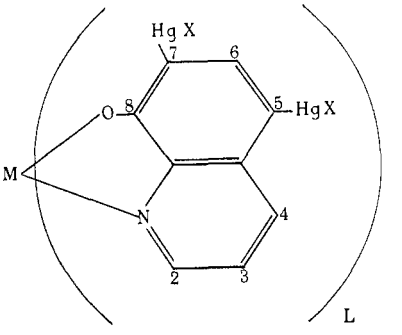

Figure 2.—Proposed structures of mercurated chelates of 8-hydroxyquinoline. M = Hg(II) or Cu(II), L = 2; M = Co(III) or Cr(III), L = 3.

Contrary to previous reports,[2,3] a 1:1 mole ratio of mercurating agent to ligand does not furnish 5-acetoxymercury(II)-8-hydroxyquinoline exclusively. The nmr spectra of the deuterated ligands derived from "monomercurated" products show a complex pattern indicative of the presence of both 5- and 7-deuterio-8-hydroxyquinolines. A mixture of *ortho*-(7-) and *para*-(5-) substituted products is expected from oxine itself but it had been believed that chelation would sterically crowd the 7 position to prevent electrophilic attack there and thus allow substitution solely at the more accessible 5 position. Our data do not allow the assessment of the relative amounts of each isomer present and it may be possible that chelation does alter the isomer distribution through steric effects, but some 7 substitution most certainly occurs.

The inertness of the pyridine ring to substitution was maintained in the metal chelates. No evidence for substitution in the pyridine ring part of the oxine ligand was detected even under the forcing conditions used.

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