

7-Iodo-8-Quinolinol from 5-Amino-8-quinolinol *via* a Gattermann Reaction (1)

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Halogeno-8-quinolinols have been of interest as metal ion precipitants, since the reports of Hahn (2) and Berg (3). This class of compounds has also played an important role in our studies of the mechanism of antifungal action of the 8-quinolinols and their copper (II) chelates (4-6) and in further relating chelation to fungitoxication (7). As part of our program, it became necessary to examine methods of preparation of halogenated 8-quinolinol (8,9).

In a study of the metal chelating properties and proton magnetic resonance spectra of 5-halo-8-quinolinols, Beimer and Fernando (10) employed the Sandmeyer reaction for the preparation of the chloro and bromo compounds and rightly avoided this approach in preparing the iodo derivatives. Irving (11) attempted to prepare 5-iodo-8-quinolinol from 5-amino-8-quinolinol by means of a Sandmeyer reaction and obtained a product which possessed the correct elemental composition but melted at 113-114°. This was lower than the reported values which ranged from 120-125° (12). A definite structure was not assigned to the compound.

Since the preparation of 7-iodo-8-quinolinol had been recently reported (8) and the properties of Irving's compound seemed to approximate this product, it was of interest to re-examine the effect of iodide on 5-diazonium-8-quinolinolium sulfate, and the conditions of the Gattermann reaction were employed (8). A comparable reaction was performed on 7-diazonium-8-quinolinolium sulfate, as prepared by nitration of 8-quinolinol-5-sulfonic acid (13), desulfonation with 15% sulfuric acid in acetic acid, reduction (5), and diazotization (8). Both 5- and 7-iodo-8-quinolinols were also subjected to the conditions of the Gattermann reaction in order to observe the effects of this reaction on the stability of the iodo substituent. The composition of each reaction mixture was determined gas chromatographically using a 1% Apiezon L column (9). The data of Table I show that under the conditions of the Gattermann reaction, 5-iodo-8-quinolinol underwent extensive deiodination and no rearrangement, while 7-iodo-8-quinolinol gave no rearrangement to the 5-iodo isomer and only 1% deiodination. 5-Amino-8-quinolinol yielded a mixture composed of 56% 7-iodo-8-quinolinol, 37% 8-quinolinol, and small quantities of 5-iodo and 5,7-diiodo-8-quinolinols, and 7-amino-8-quinolinol afforded only 8-quinolinol in very low

SCHEME 1



yield. The 60 Mhz nmr spectral features of 5- and 7-iodo-8-quinolinol, 5- and 7-nitro-8-quinolinol, and 5- and 7-amino-8-quinolinol taken in  $d_6$ -DMSO using tetramethyl silane as the interval standard are listed in Table II.

In view of the results of the Gattermann reaction on both 5- and 7-amino-8-quinolinols, and the absence of rearrangement products from 5- and 7-iodo-8-quinolinols, when treated under the conditions of the Gattermann reaction, it seems that 7-iodo-8-quinolinol was obtained from 5-amino-8-quinolinol by the rearrangement of an intermediate prior to iodination.

Diazonium salts in acidic polar media often react by a heterolytic mechanism, the intermediate being the aryl cation, after the loss of nitrogen (14). Scheme I indicates a possible mechanism for the formation of 7-iodo-8-quinolinol from 5-amino-8-quinolinols. This entails a 1,3 hydride shift on the aryl cation, after the loss of nitrogen from the diazonium salt, followed by nucleophilic attack by the iodide ion.

TABLE I

Effect of Conditions of Gattermann Reaction on 5-Amino, 7-Amino, 5-Iodo, and 7-Iodo-8-quinolinols

Starting Compound (substituted Ox (a))	Products, % (as free ligands)			
	Ox	5-IOx	7-IOx	5,7-I <sub>2</sub> Ox
5-NH <sub>2</sub>	37	3	56	4
7-NH <sub>2</sub>	100 <sup>a</sup>	0	0	0
5-I	40	60	0	0
7-I	1	0	99	0

(a) Only 8-quinolinol obtained in 2.8% yield.

TABLE II  
Proton Chemical Shifts for 5- and 7-Iodo, 5- and 7-Amino, and 5- and 7-Nitro-8-quinolins (a)  
(TMS Internal Standard)

Proton	5-IOx (b) ppm ( $\tau$ )	7-IOx ppm ( $\tau$ )	5-NH <sub>2</sub> Ox ppm ( $\tau$ )	7-NH <sub>2</sub> Ox ppm ( $\tau$ )	5-NO <sub>2</sub> Ox ppm ( $\tau$ )	7-NO <sub>2</sub> Ox ppm ( $\tau$ )
2	0.97 (quartet, $J_{23} = 4, J_{24} = 1.5$ )	0.99 (quartet, $J_{23} = 4, J_{24} = 1.5$ )	1.08 (quartet, $J_{23} = 4, J_{24} = 1.5$ )	1.23 (quartet, $J_{23} = 5, J_{24} = 1.5$ )	0.6 - 1.00 (unresolved multiplet)	0.87 (quartet, $J_{23} = 2, J_{24} = 5$ )
3	2.30 (quartet, $J_{32} = 4, J_{34} = 8$ )	2.25 (quartet, $J_{32} = 4, J_{34} = 9$ )	2.48 (quartet, $J_{32} = 4, J_{34} = 8$ )	2.80 (quartet, $J_{32} = 5, J_{34} = 8$ )	2.10 (quartet, $J_{32} = 4, J_{34} = 9$ )	2.13 (quartet, $J_{32} = 5, J_{34} = 8$ )
4	1.52 (quartet, $J_{42} = 1.5, J_{43} = 8$ )	1.61 (quartet, $J_{42} = 1.5, J_{43} = 9$ )	1.37 (quartet, $J_{42} = 1.5, J_{43} = 8$ )	1.83 (quartet, $J_{42} = 1.5, J_{43} = 8$ )	0.6 - 1.00 (unresolved multiplet)	1.41 (quartet, $J_{42} = 2, J_{43} = 8$ )
5		2.95 (doublet, $J_{56} = 8$ )		2.78 (singlet)		2.47 (doublet, $J_{56} = 9$ )
6	2.40 (doublet, $J_{67} = 9$ )	1.90 (doublet, $J_{65} = 8$ )	3.02 (doublet, $J_{67} = 8$ )	2.78 (singlet)	1.40 (doublet, $J_{67} = 9$ )	1.87 (doublet, $J_{65} = 9$ )
7	2.67 (doublet, $J_{76} = 9$ )		3.28 (doublet, $J_{76} = 8$ )		2.78 (doublet, $J_{76} = 9$ )	

(a) Spectra taken on 3% solutions of free base in d<sub>6</sub>-DMSO. (b) Ox = 8-quinolinol

It should be mentioned, at this point, that the preparation of 7-iodo-8-quinolinol from 7-amino-8-quinolinol, as previously reported (8), was, in fact, the same rearrangement as herein studied. This resulted from the attempted formation of 7-amino-8-quinolinol by nitration of 5-iodo-8-quinolinol followed by deiodination and reduction (5). The nitration step yielded the unexpected product, 5-nitro-7-iodo-8-quinolinol. The latter rearrangement will be the subject of another report.

#### EXPERIMENTAL (15)

##### 7-Nitro-8-quinolinol-5-sulfonic Acid.

The title compound was prepared (13) in 70-74% yield, m.p. 168° dec. [lit. m.p. 286° (16)].

##### 7-Nitro-8-quinolinol.

A suspension of 211 g. (0.78 mole) of 7-nitro-8-quinolinol-5-sulfonic acid in a mixture of 687 g. acetic acid and 123 g. of sulfuric acid was heated under reflux with stirring for 20 hours. A clear solution formed which was poured onto 2 l. of ice. The pH was adjusted to 5 with ammonium hydroxide and the 7-nitro-8-quinolinol was removed by filtration. The product was resuspended in water and neutralized with sodium bicarbonate, after which it was filtered off washed with water and dried at 70°, overnight. The yield of compound was 117 g. (79%). An analytical sample was crystallized from methanolic DMF, m.p. 165-166°.

*Anal.* Calcd. for  $C_9H_6N_2O_3$ : C, 56.85; H, 3.18; N, 14.73. Found: C, 56.99; H, 3.25; N, 14.43.

##### 7-Amino-8-quinolinol Hemisulfate.

A suspension of 57 g. (0.3 mole) of 7-nitro-8-quinolinol and 450 mg. platinum oxide in 150 ml. of DMF was shaken under 5 atmospheres of hydrogen. After 0.9 mole of hydrogen had been taken up, the catalyst was removed by filtration, and the filtrate was acidified with 15 g. (0.15 mole) of concentrated sulfuric acid, and an equal volume of acetone was added. The product was removed by filtration and washed (acetone) until the washings were nearly colorless. The yield of compound was 58 g. (92%), and an analytical sample was prepared by dissolution in a mixture of methanol and water followed by precipitation with acetone, m.p. 205° dec.

*Anal.* Calcd. for  $C_{18}H_{18}N_4O_6S \cdot H_2O$ : C, 49.54; H, 4.62; N, 12.84; O, 25.66; S, 7.34. Found: C, 49.41; H, 4.79; N, 12.71; O, 25.92; S, 7.61.

##### Gattermann Reaction on 5-Amino-8-quinolinol.

5-Amino-8-quinolinol sulfate (5) (25.8 g., 0.1 mole) was dissolved in a mixture of 75 ml. of water, 75 g. of ice, and 100 ml. of 47% hydriodic acid. The temperature was brought to 0° by external cooling and a solution of sodium nitrite (14.5 g., 0.21 mole) in 15 ml. of water was added with stirring over 15 minutes. Stirring was continued for an additional hour, after which 200 mg. of copper powder was added. The mixture was heated slowly to boiling and boiled until nitrogen evolution ceased. The pH was adjusted to 7 with sodium hydroxide and the product was steam distilled until crystallization no longer was observed in the condenser. The distillate was extracted several times with chloroform. On evaporation of the chloroform, 7 g. of residue remained, m.p. 100-118°. The

composition of this mixture, as obtained by gas chromatography of the trimethyl silyl derivatives (17), is shown in Table I. Upon sublimation of the mixture followed by several recrystallizations from 70% ethanol, 1.9 g. (7%) of 7-iodo-8-quinolinol was obtained, m.p. 112-113°.

##### Gattermann Reaction on 7-Amino-8-quinolinol.

7-Amino-8-quinolinol hemisulfate (20.9 g., 0.1 mole) was treated as above. A yield of 0.4 g. (2.8%) of 8-quinolinol was obtained, m.p. 74-76°. A mixed melting point with authentic 8-quinolinol showed no depression, and the ir spectra of both materials were also identical.

##### Gattermann Reaction Conditions on 5- and 7-Iodo-8-quinolinol.

One-tenth mole of the respective iodoquinolinol was dissolved in a mixture of 15 ml. of water and 10 ml. of 47% hydriodic acid. A solution of 0.02 mole of sodium nitrite in 1.5 ml. of water was added along with 20 mg. of copper powder. The mixture was stirred and slowly heated to boiling and kept at the boiling temperature for 15 minutes. After cooling, the mixture was brought to pH 7, extracted with chloroform, and gas chromatographed as the trimethyl silyl derivatives. The results are shown in Table I.

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