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Correction of the literature citing monoiodo-8-quinolinols: a critical review

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SUMMARY
Until 1995, all papers that claimed preparation or further study with monoiodo-8-quinolinol were really working with the 7-iodo isomer. Of the 83 relevant citations 67 dealt with incorrect structural assignments, 13 were critiqued due to errors made in synthesis and interpretation, and 9 had the correct structural assignments. This literature review made the following conclusions apparent. 1. Prototropic forms of 8-quinolinol influence orientation of electrophiles. 2. Under strong acidic conditions, the 5 position is favored. 3. Under mild acidic conditions, mixtures of 5 and 7 substituted compounds are formed. 4. Under basic conditions, the incoming electrophile favors the 7 position. 5. When the phenolic group is etherified or complexed with metals, only 5 substitution takes place, and 7 substitution occurs only after the 5 position is filled. 6. NXS is generally a superior halogenating agent than elemental halogen. 7. In order to avoid rearrangements, the more electronegative group should be put into the desired position followed by the less electronegative substituent.

KEY WORDS: 5-iodo-8-quinolinol; 7-iodo-8-quinolinol; 5-iodo-2-methyl-8-quinolinol; 7-iodo-2-methyl-8-quinolinol.

INTRODUCTION
A monoiodo-8-quinolinol (m.p. 127-128°C) was first reported by Matsumura in 1927. Although no proof of structure was claimed, it was believed to be 5-iodo-8-quinolinol by analogy with the corresponding 5-chloro and 5-bromo analogues [1]. Upon reacting 8-quinolinol with iodine in alcohol Pirrone and Cherubino (1939) reported a product that melted at 125-127°C and appeared to be the same as that of Matsumura. A second product (m.p. 114-116°C) was claimed to be the dehydrated form of the higher melting compound [2, 4]. It was shown by Delaby and Charonnat (1934) that iodination of 8-quinolinol with iodine monochloride in chloroform afforded a 73% yield of "5-iodo-8-quinolinol" and in acetic acid the yield was 81% [3]. Gleu and Jagemann (1939) showed that when 8-quinolinol was iodinated with iodine monochloride in aqueous pyridine a compound melting at 135°C was obtained and was reported as "5-iodo-8-quinolinol" [5]. In 1944 Ghosh, Lasker, and Banerjee treated 8-quinolinol with iodine monochloride in aqueous alcohol and obtained 92% "5-iodo-8-quinolinol" m.p. 123-124°C [6]. Coll and Coll (1951) and Luis and Coll (1951) prepared "5-iodo-8-quinolinol" by reacting 8-quinolinol with potassium triiodide in alcohol. The product was obtained in 82% yield, m.p. 125-126°C [7, 8]. Of particular interest is a procedure attributed to Irving who carried out a Sandmeyer reaction on 5-amino-8-quinolinol. A product was obtained melting at 113-114°C. It was identified as a monoiodo-8-quinolinol, but no structure was assigned to it [9].

In 1995 Crespi et al. prepared a monoiodo-8-quinolinol that melted at 135°C. The method of preparation was similar to that of Matsumura [1]. It was assigned the structure 7-iodo-8-quinolinol based on the 1H decoupled 13C NMR spectrum [65]. It should be noted that Gershon, McNeil, and Grefig (1969) had prepared a monoiodo-8-quinolinol (m.p. 112-113°C) which was thought to be "7-iodo-8-quinolinol" in contrast...
to what was accepted as 5-iodo-8-quinolinol [34]. An x-ray crystal structure determination of the compound melting at 127-128°C was reported by Shoja, Gershon, and Clarke (1997) [66]. It confirmed the veracity of the structure as reported by Crespi et al. [65]. Since the halogenation of 2-methyl-8-quinolinol paralleled that of 8-quinolinol, it was of interest to determine the accuracy of the structures assigned to 5- and 7-iodo-2-methyl-8-quinolinols [30,46]. A comprehensive study of halogenation of 2-methyl-8-quinolinol paralleled that structure as reported by Clarke et al. in 1998 [68]. These results were also in agreement with those of Crespi et al. [65].

DISCUSSION

We have been able to locate 83 reports that are relevant to this study. It should be remembered that until 1995 [65] the readily available monoiodo-8-quinolinol was accepted to be the 5-iodo analogue, and workers should not be faulted because it was inconceivable that a compound in such long and wide use would have a structure that was assigned incorrectly. This iodo-8-quinolinol was available commercially or by preparation by methods similar to that of Matsumura [1].

Since the structures of 5- and 7-iodo-8-quinolinols and 5- and 7-iodo-2-methyl-8-quinolinols were rigorously established [65,66,68], melting points alone are needed to identify the individual analogues. All four compounds have appeared in the literature, and by reversing the published melting points of the 5- and 7-iodo compounds, a set of melting points is available for the easy identification of the individual 8-quinolinols: 5-iodo, 112-113°C [38], 7-iodo, 126-127°C [1], 5-iodo-2-methyl, 88-89°C [41], and 7-iodo-2-methyl, 151-153°C [41].

There are essentially two types of studies that involved the monoiodo-8-quinolinols. The first were concerned with the synthesis and characterization of the compounds, and the others are those that employed the preformed compounds for further studies. It is obvious that until 1995, all papers reporting work with "5-iodo-8-quinolinol" were really getting results due to 7-iodo-8-quinolinol.

CRITIQUE

It is interesting that in refs. 2 and 4 melting points are reported that are suggestive of 5-iodo-8-quinolinol (114-116°C), 7-iodo-8-quinolinol (124-126°C) and impure 5,7-diiodo-8-quinolinol (185-187°C). These compounds were not recognized as such. In a private communication of Irving to Hollingshead [9], a product that melted at 113-114°C was reported. It was prepared by a Sandmeyer reaction on 5-amino-8-quinolinol. Since its melting point was not in agreement with the melting point of the compound of Matsumura [1], the work was not reported in the open literature. The compound was in fact, 5-iodo-8-quinolinol. Chawla and Jones reported the iodination of bis(8-quinolinolato) copper(II) in chloroform with a 2.3 fold molar excess of elemental iodine based on 8-quinolinol. The products obtained on removal of the copper(II) were 6.6 percent 5,7-diiodo and 6.5 percent 7-iodo-8-quinolinols based on melting points [19]. Prasad et al. iodinated the copper(II) complex of 8-quinolinol in chloroform using N-iodosuccinimide (NIS). The copper(II) complex was reported to yield 50 percent "5-iodo-8-quinolinol". It was claimed that the IR and NMR spectra matched those of an authentic sample [20]. The authentic sample was probably based on Matsumura's iodo-8-quinolinol which we now know to be 7-iodo-8-quinolinol. 7-Nitro-8-quinolinol (mp. 152°C) was reported by Gershon [26]. Neither was gas chromatography (GC) used to assay the material nor were NMR spectra obtained. Later work showed that 5-nitro-8-quinolinol melted at 174-176°C [38] and the 7-nitro analogue melted at 165-166°C [39]. These results would suggest that the product melting at 152°C was a mixture of 5- and 7-nitro-8-quinolinols, since the elemental compositions were the same for all three materials.

Since no sample of the original nitro-8-quinolinol (mp 152°C) was available at this time a series of mixtures of authentic samples of was prepared. Melting points were taken and plotted vs composition (Figure 1). The compositions were verified by H nmr, and it was found that the nitro compound melting at 152°C was consistent with that of approximately a 1:1 mixture of 5- and 7-nitro-8-quinolinols. This mixture was formed by nitrating 7-iodo-8-quinolinol, which was believed to be the 5-iodo isomer followed by deiodination [26]. Thus the 5-position was open to nitration and the 7-nitro analogue could have been formed by displacement of the 7-iodo substituent. Further reactions led to complications in the formation of iodo-8-quinolinols, which are dealt with later in this report. It should be mentioned that 5-nitro-8-quinolinol was known previously [26a], and 7-iodo-5-nitro-8-quinolinol was assigned the correct structure [32].

In the attempt to prepare bis(5-iodo-8-quinolinolato) copper(II), the method of Prasad et al. seemed to be
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Figure 1. Mixed Melting Point Curve of 5- and 7-Nitro-8-quinolinols.

suitable [20]. On iodination of the copper(II) biscomplex of 8-quinolinol with NIS in chloroform a product was obtained that was different from that which was considered authentic [34]. Rf values obtained by thin layer chromatography on silica gel and the IR spectra of the two complexes were different. Since it was not considered that the "authentic" sample could be incorrect, the new ligand was assigned the structure 7-iodo-8-quinolinol. Based on NMR spectra [65,68] and melting point of the iodo-8-quinolinols, we know now that it was the 5 isomer, and the compound reported by Prasad et al. [20] was really 7-iodo-8-quinolinol. What is most curious is that Chawla and Jones [19] and Prasad et al. [20] reported that 7-iodo-8-quinolinol was formed, whereas the product reported by Gershon, McNeil and Grefig [34] was 5-iodo-8-quinolinol. All three used essentially the same synthetic approach. GC analysis after correcting for the 5 and 7 positions of the iodo substituent, indicated a nearly quantitative yield of 5-iodo-8-quinolinol, and the yield obtained by isolation was 85%. The order of retention times in the GC table is correct and may contain useful data, although it may have been set that way serendipitously. For the preparation of 5-iodo-8-quinolinol, the method of choice would be that of Gershon, McNeil and Grefig [34].

The work of Maguire and Jones [34a] and Hixon and Jones [34b] indicated that with the exception of tropolone there are no authentic cases where complexation with metals alters the reaction position(s) of an aromatic ligand to electrophilic reagents. In view of this and the fact that 5-iodo-8-quinolinol was obtained by iodination of bis(8-quinolinolato) copper(II), a study was carried out on the halogenation of the free ligand 8-quinolinol in chloroform in the presence of NIS. A yield of 94% of 7-iodo-8-quinolinol was obtained by GC analysis, after correcting for the 5 and 7 analogues [35]. This showed that although the reactive positions for electrophilic substitution remain unchanged, the orientation of the entering halogen is influenced by complexation with metals.

It was desired to explore the Gattermann reaction to compare with the results of those of the Sandmeyer reaction [9]. The nitro-8-quinolinol as prepared by Gershon, m.p. 152°C [26], which is now suggested to be a mixture of 5- and 7-nitro-8-quinolinols, was reduced to amino and treated under the conditions of the
Gattermann reaction. A mixture was obtained as shown by GC was composed of 37% 8-quinolinol, 56% 5-iodo-8-quinolinol, 3% 7-iodo-8-quinolinol and 4% 5,7-diiodo-8-quinolinol. The isolated yield of 5-iodo-8-quinolinol, m.p. 112-113°C was 7%. Preformed 5-iodo-8-quinolinol was stable under the conditions of the Gattermann reaction, while 7-iodo-8-quinolinol underwent 40% deiodination under these conditions. The Reverdin type rearrangement most likely occurred during the nitration of the currently accepted 7-iodo-8-quinolinol as evidenced by the detection of both 5- and 7-iodo-8-quinolinos in the GC [37].

A study of the electrophilic iodination of 8-quinolinol was compared with that of its copper(II) complex using both elemental iodine and NIS in chloroform. The ratio of 7-iodo-8-quinolinol to its 5- isomer was 10:1 when NIS was employed to iodinate 8-quinolinol. With respect to the copper(II) complex, iodination with elemental iodine was unsatisfactory because of the known reduction of Cu(II) to Cu(I). In the presence of solvents varying from strong acid to fairly strong base and iodination with NIS, 93% sulfuric acid caused the formation of a preponderance of 5-iodo-8-quinolinol, and in diethylamine the iodine was oriented mainly to the 7 position. With elemental iodine, iodination did not take place in 93% sulfuric acid, and in diethylamine the iodo substituent entered the 7 position. It can be stated that NIS is a superior iodinating agent to elemental iodine in these iodination reactions, and the prototropic form of 8-quinolinol plays a major role in determining orientation [38].

Further studies showed that on nitration of 5-halo-8-quinolinos the Reverdin type rearrangement did take place. It was found that on nitration of 5-halo-8-quinolinos the fluoro and chloro compounds yielded only one product each, the respective 5-halo-7-nitro-8-quinolinol. 5-Bromo-8-quinolinol yielded 90% 7-bromo-5-nitro-8-quinolinol and 10% 5-bromo-7-nitro-8-quinolinol, as determined from the field and peak area due to the 6-proton. Results with 7-iodo-8-quinolinol cannot be properly interpreted because the starting product that was thought to be 5-iodo-8-quinolinol was really 7-iodo-8-quinolinol, and electrophilic nitration shows a preference for the 5-position. This is evidenced by the nitration of authentic 7-chloro-5-iodo-8-quinolinol [39] in the same manner as that for the 5-halo-8-quinolinos. The major product was 7-chloro-5-nitro-8-quinolinol with only a trace of 7-chloro-5-iodo-8-quinolinol [39]. Additional evidence to demonstrate that the Reverdin reaction took place, that was not recognized earlier, is based on the chlorination of "5-iodo-8-quinolinol" [6]. This reaction was repeated and it was shown by GC that a mixture containing 7-chloro-5-iodo-8-quinolinol, 5,7-dichloro- and 5,7-diiodo-8-quinolinols as the major products [39].

It was determined that the prototropic forms of 8-quinolinol influenced orientation of incoming electrophiles. The nature of the electrophilic agent and the solvent employed also played a role. When corrections were made for the identities of the 5- and 7-iodo-8-quinolinols it was found that on iodination of 8-methoxyquinoline with NIS the 7 position was not iodinated until the 5 position was completely iodinated, regardless of the solvent employed. Elemental iodine was ineffective as an iodinating agent in any solvent ranging from strong acid, to neutral, or to strong base [46].

Trecourt et al. reported that on deiodinating 5,7-diiodo-8-methoxyquinoline with phenyl lithium, 5-iodo-8-methoxyquinoline was obtained. The structure was identified correctly by NMR [64]. The compound reported by Gershon and Parmegiani was prepared from what is now established as 7-iodo-8-quinolinol by methylation of the phenolic group [27]. Also Trecourt et al. reported the preparation of 7-iodo-8-methoxyquinoline by reacting 7-bromo-8-methoxyquinoline with phenyl lithium followed by iodine treatment. It was established that the structure was correct by NMR spectroscopy [64]. The product of Gershon, McNeil, and Schulman was the reverse isomer [46]. Further confirmation that the etherified 8-quinolinol as the benzzyloxy compound could cause iodine to be oriented to the 5 position was by iodination with iodine in iodic acid as reported by Nakano and Imai [67] who cited Suzuki and Tamura [67a] for the method of iodination. A sample of the material was received in our laboratory, and the NMR spectra confirmed the assigned structure.

More recently we prepared 3- and 6-iodo-8-quinolinos. Their structures were determined to be correct by elemental analysis, high resolution mass spectroscopy and by NMR spectroscopy [73].

A number of 5-iodo-8-quinolinol-7-sulfonic acids were found to be incorrect [74-81]. Claims were made that 8quinolinol-7-sulfonic acid was iodinated. This was incorrect in view of the fact that Gershon and McNeil [82] showed that all previous methods for preparing 8-quinolinol sulfonic acids led to the 5-sulfonic acid, and all cases reported to be 5-iodo-8-quinolinol-7-sulfonic acid were in fact the reverse isomer.

In summary, what was learned from this literature review is that: 1. Prototropic forms of 8-quinolinol...
influence the orientation of the electrophile. 2. Under strong acidic conditions the 5 position is favored. 3. Under mild acidic, neutral, or basic conditions mixtures of 5 and 7 substituted compounds are formed. 4. Under basic conditions the incoming electrophile favors the 7 position. 5. When the phenolic group is derivatized by etherification or complexation with metals only 5 substitution takes place and no 7 substitution, until all of the 5 position is filled. 6. NXS is generally a superior halogenating agent than elemental halogen, 7. In order to avoid rearrangements the more electronegative substituent should be put into the desired position followed by the second less electronegative substituent.

**ADDENDUM**

References in which 5-iodo-8-quinolinol and 7-iodo-8-quinolinol are reversed [1-8,10-18,21-25,27-29,31,33,36,40-45,47-63,69,74-81]. References that were critiqued [9,19,20,30,32,34-39,46,64]. References that were correct [64-68,70,71,73,83].

**REFERENCES**
