Nitration of 5-Halogeno-8-quinolinols and Accompanying Reverdin Rearrangement (1)

Herman Gershon and Maynard W. McNeil

Boyce Thompson Institute for Plant Research, Inc.
Yonkers, New York 10701

Received March 8, 1971

The preparation and antifungal studies of 5-halogeno-7-nitro-8-quinolinols (2) and 7-halogeno-5-nitro-8-quinolinols (3) have been reported. It has recently been observed (4) that what was believed to have been 7-nitro-8-quinolinol (2) was, in fact, 5-nitro-8-quinolinol which was formed by nitration of 5-iodo-8-quinolinol followed by deiodination (2). As a result, a number of other products derived from this reaction sequence were reported incorrectly. Among these were 5-iodo-7-nitro-8-quinolinol (2), 7-fluoro-8-quinolinol (3), and 7-fluoro-5-nitro-8-quinolinol (3).

The present work is concerned with the unequivocal characterization of the halogenonitro-8-quinolinols, the preparation of the compounds that were reported in error, and the reexamination of the nitration of 5-halogeno-8-quinolinols.

Since nitro groups are not known to rearrange under the conditions of electrophilic halogenation, 5-nitro-8-quinolinol (5) was chlorinated (3), brominated (6), and iodinated (7) to the respective halogeno derivatives. Starting with 7-nitro-8-quinolinol (4), the 5-chloro, 5-bromo, and 5-iodo compounds were prepared by the respective halogenation procedures. The fluoronitro-8-quinolinols were made by nitration (2) of 5-fluoro-8-quinolinol (8) and of 7-fluoro-8-quinolinol, as prepared from 7-amino-8-quinolinol (4) by the Baltz-Schiemann reaction. The elemental composition of both compounds was the same, but the nmr and ir spectra showed differences. The structures of the fluoro 8-quinolinols were established by preparing and characterizing the respective fluoronitro-8-quinolinols. The 60 Mhz nmr spectral features of the halogenonitro-8-quinolinols taken in d_6-DMSO using tetramethyl silane as the internal standard are listed in Table I, and the ir spectra in potassium bromide are shown in Figures 1 and 2. It can be seen in Table I that for 7-fluoro-5-nitro-8-quinolinol, the absorption of the 4 proton is at a lower field than that of the 2 proton, and this is consistent with the shift for all of the other 7-halogeno-5-nitro-8-quinolinols. On the other hand, the absorption of the 4 proton in 5-fluoro-7-nitro-8-quinolinol is at a higher field than that of the 2 proton, and this is consistent with the shifts found in the other 5-halogeno-7-nitro-8-quinolinols. Thus it was reasonable to consider the structures assigned as being correct.

The 5-halogeno-8-quinolinols as well as 8-quinolinol were treated with concentrated nitric acid in glacial acetic acid, as previously described (2,9). The product, as obtained from each reaction, without purification, was subjected

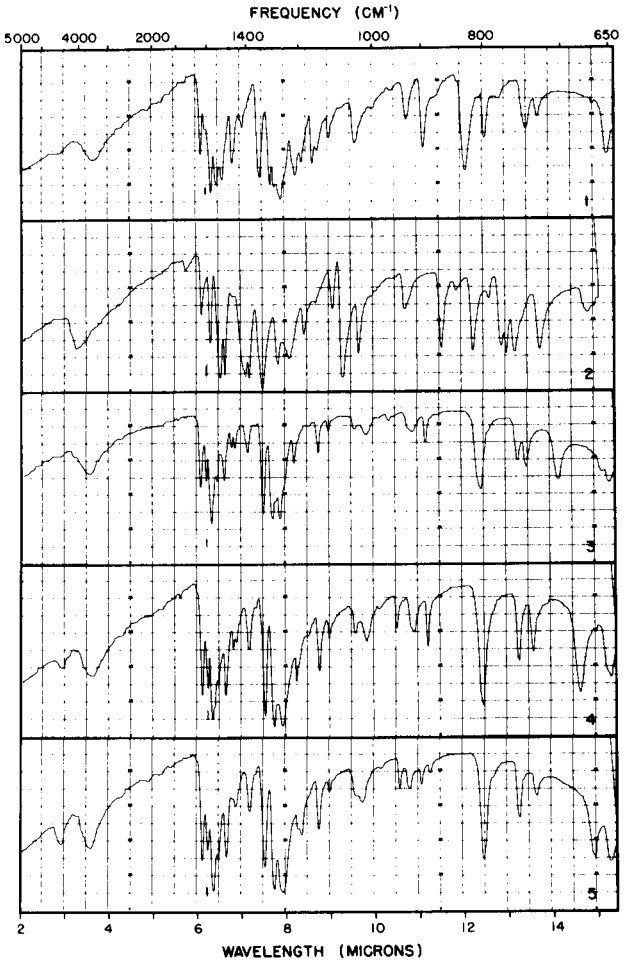

Figure 1. Ir spectra in potassium bromide of **1**: 7-nitro-8-quinolinol, **2**: 5-fluoro-7-nitro-8-quinolinol, **3**: 5-chloro-7-nitro-8-quinolinol, **4**: 5-bromo-7-nitro-8-quinolinol, **5**: 5-iodo-7-nitro-8-quinolinol.

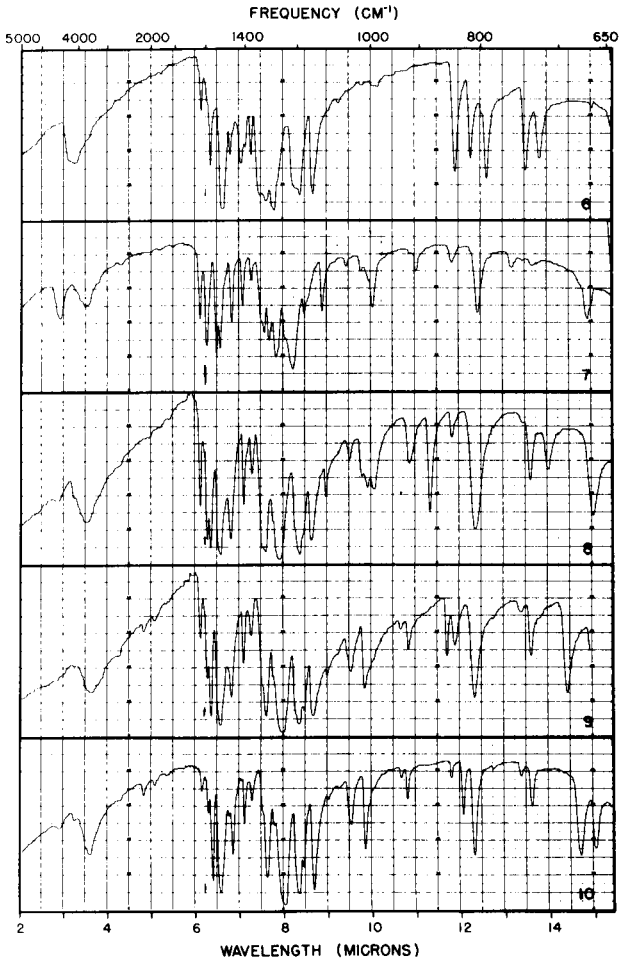

Figure 2. Ir spectra in potassium bromide of **6**: 5-nitro-8-quinolinol, **7**: 7-fluoro-5-nitro-8-quinolinol, **8**: 7-chloro-5-nitro-8-quinolinol, **9**: 7-bromo-5-nitro-8-quinolinol, **10**: 7-iodo-5-nitro-8-quinolinol.

to nmr spectrometry. The mononitro product of the nitration of 8-quinolinol was found to be 5-nitro-8-quinolinol (4). It was determined from the field and peak area due to the 6 proton that 5-fluoro and 5-chloro-8-quinolinols yielded the expected 7-nitro compounds. 5-Bromo-8-quinolinol yielded 90% 7-bromo-5-nitro-8-quinolinol and 10% 5-bromo-7-nitro-8-quinolinol, and 5-iodo-8-quinolinol yielded only 7-iodo-5-nitro-8-quinolinol. Thus it appears that not only 5-iodo-8-quinolinol rearranges during nitration, but 5-bromo-8-quinolinol also rearranges extensively as a result of nitration.

To gain further insight into this reaction, it was of interest to observe the effect of nitric acid on 7-chloro-5-iodo-8-quinolinol. It was expected that the iodine would be labile in this compound, yet, since the 7-position is blocked, the question remained as to the fate of the iodine. The starting material was prepared by iodination of 7-chloro-8-quinolinol (10). Upon treatment with nitric acid in acetic acid, the product obtained was found by gas chromatography of the trimethyl silyl derivatives to be 7-chloro-5-nitro-8-quinolinol contaminated with only a trace of 7-chloro-5-iodo-8-quinolinol. No iodo quinolinols, other than starting compound, were detected, and the melting point and spectra of the product were consistent with those of the authentic sample. The filtrate of this preparation contained elemental iodine. When one equivalent of 5-iodo-8-quinolinol was treated with 0.75 equivalents of nitric acid, a significant amount of 5,7-diiodo-8-quinolinol was formed. It should also be noted that on replacement of the one equivalent of nitric acid with the equivalent amount of hydrochloric acid in the acetic acid solution of 5-iodo-8-quinolinol and allowing the mixture to stir at 40° overnight, no disproportionation to 8-quinolinol and 5,7-diiodo-8-quinolinol took place.

It thus appears that these are further examples of the rearrangement discovered by Reverdin (11), and it is proposed that the formation of 7-iodo-5-nitro-8-quinolinol takes place by at least two reaction mechanisms. The displacement of iodine from the 5 position of 5-iodo-8-quinolinol by nitronium cation is followed by iodination of the product, 5-nitro-8-quinolinol. At the same time, iodination of 5-iodo-8-quinolinol to 5,7-diiodo-8-quinolinol also occurs. The latter product then reacts with additional nitronium cation to yield 7-iodo-5-nitro-8-quinolinol and iodine. Since the iodination reaction is comparatively rapid, it must have been brought about primarily by the freshly released I^+ and not by the iodine which was also observed. This is in agreement with the observations of Gershon *et al.*, (12) who showed that 8-quinolinol in glacial acetic acid consumed all of the iodine from an equivalent of *N*-iodosuccinimide, whereas only 18% of the iodine from iodine reacted in a comparable experiment. The formation of 7-iodo-5-nitro-8-quinolinol from the diiodoquinolinol is consistent with the mechanism proposed by Robinson (13).

Since it is now established that both 5-iodo and 5-bromo-7-nitro-8-quinolinols were incorrectly reported (2), it is also obvious that the corresponding halogeno amines were incorrect. Both 5-amino-7-bromo and 5-amino-7-iodo-8-quinolinol hydrochlorides are herein reported.

EXPERIMENTAL (11)

7-Fluoro-8-quinolinol.

The title compound was obtained from 7-amino-8-quinolinol hemisulfate (4) in 1% yield by the method previously described (3). An analytical sample was prepared by crystallization from hexane, m.p. 126-127°.

Anal. Calcd. for C_9H_6FNO: C, 66.26; H, 3.71; F, 11.65; N, 8.58. Found: C, 66.28; H, 3.71; F, 11.77; N, 8.85.

Proton Chemical Shifts for 7-Halogeno-5-Nitro and 5-Halogeno-7-Nitro-8-Quinolinols (a)
(tms Internal Standard)

Compound	Proton Chemical Shift ppm (τ) Proton 2	3	4	6
7-F-5-NO_2Ox (b)	0.88 (broad absorption, unresolved)	2.05 (broad absorption, unresolved)	0.69 (doublet J_{43} = 9)	1.35 (doublet J_{HF} = 13)
7-Cl-5-NO_2Ox	0.90 (doublet J_{23} = 5)	2.00 (quartet J_{32} = 5, J_{34} = 9)	0.55 (doublet J_{43} = 9)	1.33 (singlet)
7-Br-5-NO_2Ox	0.92 (quartet J_{23} = 5, J_{24} = 1.5)	1.95 (quartet J_{32} = 5, J_{34} = 9)	0.58 (quartet J_{42} = 1.5, J_{43} = 9)	1.08 (singlet)
7-I-5-NO_2Ox	1.05 (quartet J_{23} = 5, J_{24} = 1.5)	2.05 (quartet J_{32} = 5, J_{34} = 9)	0.73 (quartet J_{42} = 1.5, J_{43} = 9)	1.15 (singlet)
5-F-7-NO_2Ox	0.78 (quartet J_{23} = 4, J_{24} = 2)	2.05 (quartet J_{32} = 4, J_{34} = 9)	1.33 (quartet J_{42} = 2, J_{43} = 9)	2.01 (doublet J_{HF} = 11)
5-Cl-T-NO_2Ox	0.93 (quartet J_{23} = 4, J_{24} = 2)	2.10 (quartet J_{32} = 4, J_{34} = 9)	1.42 (quartet J_{42} = 2, J_{43} =9)	1.80 (singlet)
5-Br-7-NO_2Ox	0.80 (quartet J_{23} = 4, J_{24} = 2)	1.96 (quartet J_{32} = 4, J_{34} = 9)	1.32 (quartet J_{42} = 2, J_{43} = 9)	1.55 (singlet)
5-I-7-NO_2Ox	0.88 (quartet J_{23} = 4, J_{24} = 2)	2.02 (quartet J_{32} = 4, J_{34} = 9)	1.50 (quartet J_{42} = 2, J_{45} = 9)	1.38 (singlet)
5,7-$(NO_2)_2$Ox	1.02 (doublet J_{23} = 9)	1.71 (quartet J_{32} = 9, J_{34} = 6)	0.14 (doublet J_{43} = 6)	0.70 (singlet)

(a) Spectra taken on 3% solutions of free base in d_6-DMSO. (b) Ox = 8-quinolinol.

7-Fluoro-5-nitro-8-quinolinol.

7-Fluoro-8-quinolinol (1.63 g., 0.01 mole) was dissolved in 40 ml. of acetic acid and a solution of nitric acid (0.82 ml., 0.013 mole) in 5 ml. of acetic acid was added dropwise at room temperature with stirring. Agitation was continued for 1 hour after which 100 ml. of water was added to the mixture. The product was removed by filtration, washed free of acid with water, and dried at 70° overnight. The yield of compound was 1.1 g. (53%), and an analytical sample was obtained by crystallization from a mixture of methyl alcohol and DMF, m.p. 250° dec.

Anal. Calcd. for $C_9H_5FN_2O_3$: C, 51.93; H, 2.42; F, 9.13. N, 13.46. Found: C, 52.27; H, 2.73; F, 8.89; N, 13.22.

5-Chloro-7-nitro-8-quinolinol.

7-Nitro-8-quinolinol (4) (1.91 g., 0.01 mole) and potassium hydroxide (5.6 g., 0.1 mole) were slurried in a mixture of 100 ml. of water and 50 ml. of methyl alcohol. To this was added 100 ml. of 5% sodium hypochlorite, and the mixture was heated to 70° and stirred for 1 hour. After cooling, 25 ml. of acetic acid was added, and 1.9 g. (84%) of product was obtained on filtration and washing with water. The compound was crystallized from aqueous acetic acid and melted at 197-198° dec. [Lit. (9) m.p. 197° dec.].

5-Bromo-7-nitro-8-quinolinol.

A solution of 17.0 g. (0.106 mole) of bromine in 50 ml. of acetic acid was added to a solution of 19.0 g. (0.1 mole) of 7-nitro-8-quinolinol (4) in 800 ml. of acetic acid and stirred for 1 hour while maintaining the temperature at 50°. At the end of that time, 1 liter of water was added to the mixture, and the product was removed by filtration, washed free of acid, and dried at 70° overnight. A yield of 23 g. (86%) of compound was obtained, and an analytical sample was obtained by crystallization from

DMF, m.p. 194-195° dec.

Anal. Calcd. for $C_9H_5BrN_2O_3$: C, 40.18; H, 1.87; Br, 29.70; Found: C, 40.21; H, 1.87; Br, 29.58; N, 10.13.

5-Iodo-7-nitro-8-quinolinol.

To 9.5 g. (0.05 mole) of 7-nitro-8-quinolinol (4) dissolved in 200 ml. of DMF was added 9.0 g. (0.055 mole) of iodine monochloride in 50 ml. of DMF. The mixture was stirred and kept at 100° for 2 hours. After allowing it to cool to room temperature, 200 ml. of methyl alcohol followed by 300 ml. of water were added, and 12 g. (76%) of product was obtained by filtration, washing with water, and drying at 70° overnight. An analytical sample was prepared by crystallization from DMF, m.p. 233-234° dec.

Anal. Calcd. for $C_9H_5IN_2O_3$: C, 34.20; H, 1.59; I, 40.15; N, 8.86. Found: C, 34.48; H, 1.51; I, 39.89; N, 9.05.

7-Amino-5-bromo-8-quinolinol Hydrochloride.

The title compound was prepared from 5-bromo-7-nitro-8-quinolinol in 94% yield by the method previously described (2). An analytical sample was crystallized from aqueous acetone and decomposed slowly above 254°.

Anal. Calcd. for $C_9H_8BrClN_2O$: C, 39.23; H, 2.93; N, 10.17. Found: C, 39.18; H, 2.99; N, 10.20.

7-Amino-5-iodo-8-quinolinol Hydrochloride.

The title compound was prepared from 5-iodo-7-nitro-8-quinolinol in 98% yield in the same manner as the bromo analog. An analytical sample was obtained by crystallization from aqueous acetone, m.p. 212-213° dec.

Anal. Calcd. for $C_9H_8ClN_2O$: C, 33.51; H, 2.50; N, 8.69. Found: C, 33.80; H, 2.62; N, 8.59.

5-Nitro-8-quinolinol.

To a solution of 7.25 g. (0.05 mole) of 8-quinolinol in 175 ml. of acetic acid was added, dropwise with stirring, a solution of 5 ml. (0.079 mole) of nitric acid in 25 ml. of acetic acid. The mixture was kept below 30° by external cooling. After 2 hours, the insoluble 5,7-dinitro-8-quinolinol was removed by filtration, washed with water, and dried at 70° overnight. The yield of product was 1.3 g. (11.2%), m.p. 315° dec. [Lit. (12) m.p. 325° dec.). The filtrate was diluted to 1000 ml. with water and adjusted to *p*H 5-6 with sodium hydroxide. The 5-nitro-8-quinolinol was obtained by filtration, washed with water, and dried at 70° overnight. The yield of product was 4.4 g. (46%), m.p. 174-176° [Lit. (5) m.p. 180°].

7-Chloro-5-iodo-8-quinolinol.

To a solution of 18.9 g. (0.1 mole) of 7-chloro-8-quinolinol (10) and 14.7 g. (0.15 mole) of potassium acetate in 250 ml. of 95% methyl alcohol was added 24 g. (0.095 mole) of iodine in 350 ml. 95% methyl alcohol during the course of 0.5 hour with stirring. The mixture was kept under reflux for 15 minutes after the completion of addition of the iodine solution, after which 400 ml. of water was added and sufficient sodium bisulfite to discharge any residual color due to free iodine. The product (30 g., 98%) was removed by filtration, washed with water, and dried overnight. An analytical sample was obtained after 2 recrystallizations from a (1:1) mixture of DMF and methyl alcohol, m.p. 204-205° dec. [Lit. (17) m.p. 147-148°].

Anal. Calcd. for C_9H_5ClINO: C, 35.38; H, 1.65; N, 4.58. Found: C, 35.53; H, 1.45; N, 4.46.

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