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Effect of N-halosucinimides on 5-, 7- and 5,7-8-quinolinol sulfonic acids

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ABSTRACT
8-Quinolinol 5-, 7- and 5,7-sulfonic acids were treated with N-halosuccinimides (NXS) where the halogen atom was chlorine, bromine or iodine under different conditions of solvent, temperature and time. Under neutral or basic conditions the sulfonic acid group was retained while in dilute acid the SO3H group was largely displaced by halogen. Excess NXS caused additional electrophilic substitution. Mild hydrolysis of 5-iodo-8-quinolinol-7-sulfonic acid and 7-iodo-8-quinolinol-5-sulfonic acid with 15% sulfuric acid in acetic acid formed the 5- and 7-iodo-8-quinolinol respectively in high yield.

KEYWORDS: 5-iodo-8-quinolinol, 7-iodo-8-quinolinol, 5-, 7- and 5,7-8-quinolinol sulfonic acids, reaction with NXS

INTRODUCTION
We have found that methods employing N-halosuccinimides (NXS) where X = Cl, Br, or I were superior halogenating agents to the classical methods using elemental halogens. Mixed halogen containing agents were not as convenient or effective. Since 5-, 7- and 5,7-8-quinolinol sulfonic acids were available [1] as well as a number of halogenated products of the 8-quinolinol sulfonic acids prepared by different halogenating agents, we did a study comparing the NXSs with other halogenating agents. The object was to determine conditions of halogenation and formation of by products [2-5]. A review of the literature described the preparation of halo-8-quinolinol sulfonic acids and some by products [6]. Other studies on the halogenation of 8-quinolinol, its copper(II) biscomplex and 8-methoxyquinoline, showed that the prototropic form, temperature, concentration of halogen and solvent medium control the orientation of the incoming halogen [2, 7, 8]. The data here are a compilation of results obtained at different times rather than a systematic study. However it yields conclusions regarding the orientation of incoming electrophiles, and the displacement of sulfonic acid substituents under certain conditions.

MATERIALS AND METHODS
All compounds in this study are in Table 1 and are identified by reference. Their structures are shown in Schemes 1-3. It should be noted that the results obtained in the present work are based on isolated product yields and not on identifications of materials resulting from gas chromatographic data [2, 7, 8]. Since all of the products in this study were known, identifications were made by melting points, mixed melting points and in many cases by 1H NMR spectra. Methods employed in carrying out these reactions are found in the corresponding references in Table 1. This work is concerned with 8-quinolinols in which the sulfonic acid substituents are in the 5, 7, or 5,7 positions. Washings of reaction mixtures were evaporated in most cases, and residues were identified.

*Deceased Feb 5, 2007
Table 1. Halogenation of 8-quinolinol sulfonic acids with N-halosuccinimides (NXS). X = Cl, Br, I and other halogenating agents.

<table>
<thead>
<tr>
<th>8-Quinolinol-sulfonic acids and substituents</th>
<th>Ratio of NXS to substrate</th>
<th>Solvent medium, temperature</th>
<th>Sulfonic acid, substituents, yield, mp</th>
<th>Quinoline byproducts, substituents, yield, mp</th>
<th>Other method, sulfonic acid, yield, mp</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3-Cl-5-SO$_3$H (1a) [2]</td>
<td>NCS = 1:1</td>
<td>H$_2$O (KOH), pH 7, r.t., 0.5 h</td>
<td>3,7-Cl$_2$-5-SO$_3$H (2) [2], 85%, 322-5$^\circ$ dec</td>
<td>3,5,7-Cl$_3$, (3) [2], 9%, 149-150$^\circ$</td>
<td>NONE</td>
</tr>
<tr>
<td>-6-Cl-5-SO$_3$H (1b) [5]</td>
<td>NCS = 1:1</td>
<td>H$_2$O (KOH), pH 7, r.t., 0.5 h</td>
<td>6,7-Cl$_2$-5-SO$_3$H (4), 66%, 182-3$^\circ$ dec</td>
<td>5,6,7-Cl$_3$ (4a) [5], 20%, 213-214$^\circ$</td>
<td>NONE</td>
</tr>
<tr>
<td>-5-SO$_3$H (5a) [2] $^a$</td>
<td>NBS = 1:1</td>
<td>H$_2$O (KOH), pH 7, r.t., 0.5 h</td>
<td>7-Br-5-SO$_3$H (5f) [2], 95%, 280-2$^\circ$ dec.</td>
<td>NONE</td>
<td>H$_2$O (KOB)$_r$, pH 7 [2], 66%, 280$^\circ$ dec.</td>
</tr>
<tr>
<td>-5-SO$_3$H (5a) [2] $^a$</td>
<td>NBS = 2:1</td>
<td>CH$_3$CN, AcOH (1:1), heat 60$^\circ$, 10 min</td>
<td>NONE</td>
<td>5,7-Br$_2$, (6), [6], 100%, 202-7$^\circ$</td>
<td>NONE</td>
</tr>
<tr>
<td>-7-SO$_3$H (5b) [1] $^a$</td>
<td>NBS = 2:1</td>
<td>CH$_3$CN, AcOH (1:1), heat 60$^\circ$, 10 min</td>
<td>NONE</td>
<td>5,7-Br$_2$ (6), [6], 89%, 195-196$^\circ$</td>
<td>NONE</td>
</tr>
<tr>
<td>-5,7-(SO$_3$H)$_2$ (5c) [1] $^b$</td>
<td>NBS = 1:1</td>
<td>CH$_3$CN, AcOH (1:1), heat 60$^\circ$, 10 min</td>
<td>NONE</td>
<td>5,7-Br$_2$ (6), [6], 48%, 195$^\circ$</td>
<td>NONE</td>
</tr>
<tr>
<td>Compound</td>
<td>NBS</td>
<td>Reaction Conditions</td>
<td>Yield</td>
<td>Products</td>
<td></td>
</tr>
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<td>----------</td>
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<tr>
<td>-3-Br-5-SO₃H (5d) [3]</td>
<td>NBS = 1:1</td>
<td>H₂O (KOH), pH 7, r.t., 0.5 h</td>
<td>56%, 320-1°C dec</td>
<td>acetone washings not evaporated</td>
<td></td>
</tr>
<tr>
<td>-6-Br-5-SO₃H (5e) [3]</td>
<td>NBS = 1:1</td>
<td>H₂O (KOH) pH 7, r.t., 0.5 h</td>
<td>54%, 194-8 dec</td>
<td>acetone washings not evaporated</td>
<td></td>
</tr>
<tr>
<td>-7-Br-5-SO₃H (5f) [9]</td>
<td>NBS = 1:1</td>
<td>95% aq CH₃OH, r.t., 7 days</td>
<td>66%, 290-300 dec</td>
<td>5-Br₂Ox (6), [6], 10%, 196°C</td>
<td></td>
</tr>
<tr>
<td>-7-SO₃H (5b) [1]</td>
<td>NIS = (1:1)</td>
<td>95% aq CH₃OH, r.t., 24 h</td>
<td>89%, 274-5°C dec</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>-5-I-7-SO₃H (9g) [1]</td>
<td>NONE</td>
<td>15% H₂SO₄, AcOH (w/v), heat until in solution</td>
<td>NONE</td>
<td>5-IOx (12) [11], 90%, 107-8°C, Ox (11), [5]</td>
<td></td>
</tr>
<tr>
<td>-7-I-5-SO₃H (9d)</td>
<td>NONE</td>
<td>15% H₂SO₄, AcOH (w/v), heat 25 h</td>
<td>NONE</td>
<td>7-IOx (10) [11], 72%, 122-3°C, Ox (11), [5]</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Where no reference is given, the work was not previously reported.
- Lit m.p. 195-6 [6, p 711]
- Ox = 8-quinolinol
- 5- and 7-iodo-8-quinolinols after corrections of previously assigned structures [9-11]
RESULTS

When 3-chloro (1a) or 6-chloro-8-quinolinol-5-sulfonic acids (1b) in the anionic form were further chlorinated with NCS at room temperature the 7-substituted products were obtained along with significant yields of byproducts 3,5,7- (3a) and 5,6,7-trichloro-8-quinolinols(4a). Similarly upon bromination with NBS, 8-quinolinol-5-sulfonic acid (Sa) yielded 95% of the 7-bromo product (Sf) and no by-product. By treating the 8-quinolinol-5-sulfonic acid (Sa) with two equivalents of NBS to one of substrate in a mixture of acetonitrile, acetic acid (1:1) no sulfonic acid was obtained, and 100% of 5,7-dibromo-8-quinolinol (6) was the sole product. The 7-sulfonic acid (5b) under the same conditions yielded 84% of 6. 8-Quinolinol-5,7-disulfonic acid (5e) when treated with NBS in (1:1) ratio in the same solvent mixture afforded (6) in 48% yield, and no other products were obtained. Upon bromination 3-bromo (5d) and 6-bromo-8-quinolinol-5-sulfonic acid (5e) in the anionic forms, the 7-bromo products 5g and 5h formed in 56% and 64% respectively. Not having worked up the washings might explain the relatively low yields of sulfonic acids.

When 7-bromo-8-quinolinol-5-sulfonic acid (5f) was treated with NBS (1:1) in 95% aqueous methanol for seven days at room temperature, 66% 5g and 10% 5,7-dibromo-8-quinolinol (6) were obtained. Upon reacting 8-quinolinol-5-sulfonic acid (5b) with NIS (1:1) in aqueous methanol 89% 5-iodo-8-quinolinol-7-sulfonic acid (9g) was obtained. Using the same procedure with iodine monochloride in place of NIS 72% of 9g was formed. Hydrolysis of 9g with 15% sulfuric acid in acetic acid with heating until all of the substrate went into solution, yielded 90% 5-iodo-8-quinolinol (12) and 10% of 11. When
Halo-8-quinolinols and sulfonic acids

Scheme 2

5a: E = SO₃H; A, C, D = H
5b: D = SO₃H; A, C, E = H
5c: E, D = SO₃H; A, C = H
5d: E = SO₃H; A = Br, C, D = H
5e: E = SO₃H; C = Br; A, D = H
5f: E = SO₃H; D = Br; A, C = H
5g: E = SO₃H; A, D = Br; C = H
5h: E = SO₃H, C, D = Br; A = H
7-ido-8-quinolinol-5-sulfonic acid (9) was the substrate and heated three hours as 9g, the products were 72% 7-ido-8-quinolinol (10) and 7% of 11.

**DISCUSSION**

The sulfonic acid group has often been used as a protective group in the synthesis of aromatic compounds because it is readily replaced by H⁺ on heating in dilute acid solution. It can also be replaced by electrophiles other than H⁺, e.g. Br⁺ and Cl⁺. Thus treatment with NCS or NBS in dilute acid solution leads to replacement of the SO₃H group by halogen. Examples in this work are 1a to 2, 1b to 4, (cf Scheme 1) 5a to 5f, 5d to 5g, and 5e to 5h (cf Scheme 2). The yield of by-products is distinctly greater with NCS than with NBS. This suggests that under altered reaction conditions NCS might yield fewer side products.

While Cl or Br substituents on an aromatic ring are not readily replaced by an entering electrophile, an iodo substituent may be replaced. Thus on removal of a SO₃H group under conditions where Cl or Br substituents are unaffected, iodine can be removed, e.g. by heating for 24h in 15% H₂SO₄, acetic acid (1:1) 7-ido-8-quinolinol 5-sulfonic acid (9) is converted to 8-quinolinol (11). However on heating 9 for 3h, iodine is retained to give 7-ido-8-quinolinol (10) in 90% yield. Similarly 5-ido-8-quinolinol-7-sulfonic acid (9g) is converted to 5-ido-8-quinolinol (12) in 72% yield (cf Scheme 3 and Table 1).
REFERENCES