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Effect of Dimethyl Sulfoxide and Dimethylformamide on the Stability of 4-Halo-8-quinolinols

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Summary. Polyhalo-8-quinolinols with chlorine or bromine in position 4 were not stable in *DMSO* or *DMF*. The degradation product from 4,5-dichloro-8-quinolinol was 5-chloro-4,8-quinolindiol and the major product from 4,5-dibromo-8-quinolinol was 3,5-dibromo-4,8-quinolindiol. 4,5,7-Trichloro- and 4,5,7-tribromo-8-quinolinols yielded similar hydrolytic products, and for the bromo compound, a rebrominated product in *DMSO*. In *DMF* rebromination did not occur. In pyridine-d_5 these reactions did not take place, indicating a special ability of *DMSO* and *DMF* to cause such hydrolysis at position 4 of 4-halo-8-quinolinols.

Keywords. Degradation of 4-halo-8-quinolinols in *DMSO* and *DMF*; 4-Halo-8-quinolinols stable in pyridine-d_5; 5-Chloro-4,8-quinolindiol; 5-Bromo-4,8-quinolindiol; 3,5-Dibromo-4,8-quinolindiol.

Introduction

In studying the antifungal properties of polyhalogenated 8-quinolinols, we noted that 4-halo compounds were unstable in dimethyl sulfoxide (*DMSO*) solution because the minimum inhibitory concentrations (MICs) were not reproducible in solutions that had aged. The lability of the 4 position in these compounds was also implicated by ^{1}H and ^{13}C NMR spectroscopy. Freshly prepared solutions of the 4-halo analogues in *DMSO* had to be employed [1–3] to overcome this problem. It was of interest to determine how the 4-halo-8-quinolinols changed in *DMSO* solution. It was of further interest to determine if other solvents showed the same behavior as did *DMSO*.

Results and Discussion

Solutions of each compound that had aged in *DMSO* for several weeks or longer were combined, and the dissolved matter was recovered by precipitation with

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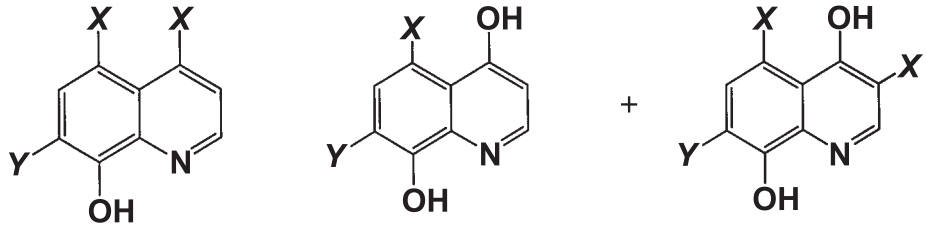


1 X = Cl, Y = H
2 X = Br, Y = H
3 X = Cl, Y = Cl
4 X = Br, Y = Br

1a X = Cl, Y = H
2a X = Br, Y = H
3a X = Cl, Y = Cl
4a X = Br, Y = Br

2b X = Br, Y = H
4b X = Br, Y = Br

Fig. 1. Compounds **1**–**4** and some of their degradation products (**1a**–**4a**, **2b**, and **4b**)

water, and air drying. The crude solids were subjected to ^{1}H and ^{13}C NMR spectroscopy as well as to high resolution mass spectroscopy (HRMS). Some of the products identified by HRMS in aged solutions of the 4-halo-8-quinolinols in *DMSO* are shown in Fig. 1. Compounds **1**–**4** are starting materials. The product **1a** derived from an aged *DMSO* solution of **1** was characterized as 5-chloro-4,8-quinolinediol by ^{1}H and ^{13}C NMR. The product from the equivalent bromo compound **2** was shown to be primarily the previously unknown 3,5-dibromo-4,8-quinolinediol **2b**.

The HRMS spectra of products from the four *DMSO* solutions showed the absence of, or at most traces of the starting materials **1**–**4**. The solution from **1** contained nearly pure **1a**, a hydrolytic product. The solution from **2** contained **2b**, a product of hydrolysis and rebromination at position 3, and a lesser amount of the hydrolytic product **2a**. Compounds **3** and **4** yielded products similar to those from **1** and **2**. The mass spectra contained fragmentation products in addition to the parent compounds.

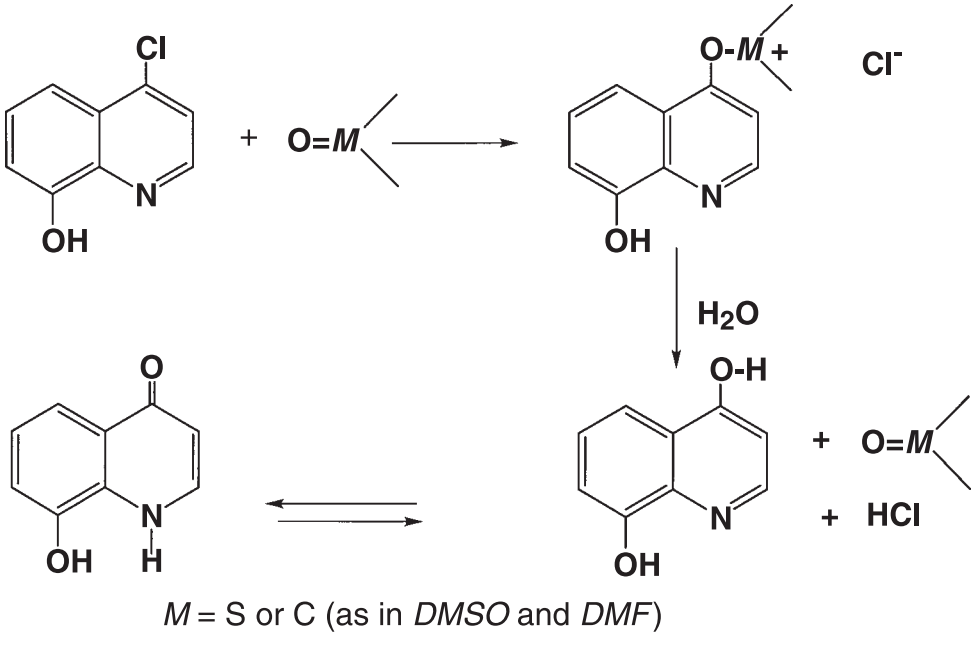
Halogenation at position 3 of 4-hydroxyquinolines has been reported previously [4]. Both chlorination and bromination were observed under electrophilic conditions. In the present study only bromination, and no chlorination, was observed. It appears that the reactions in this study are mechanistically different from those observed earlier [4]. It is thus apparent that the erratic results in MICs were reflected in the ^{1}H and ^{13}C NMR spectra which had changed in solutions of **1**–**4** that had aged in *DMSO*.

To determine if other solvents would cause similar reactions to those in *DMSO*, we examined solutions in CD_3CN, $(CD_3)_2CO$ and $CDCl_3$ by ^{1}H NMR. Because the samples were quite insoluble in these solvents, ^{1}H NMR spectra could only be measured in heated solutions, and the solutes precipitated by the end of the run. These solvents were not suitable for such an ageing study. Solutions of **1**–**4** in pyridine were stable for at least one week and gradually precipitated from solution because the solvent absorbed water. Solutions in dimethylformamide (*DMF*-d_7) were stable for more than one week, whereas those in *DMSO*-d_6 showed changes in the ^{1}H and ^{13}C NMR spectra within one to two days. However on longer standing, the compounds in solution in *DMF* did hydrolyze.

Samples **2** and **4**, which contain bromine, decomposed more rapidly than the chlorine containing ones **1** and **3**. Thus, *DMSO* appears to assist in the hydrolysis. An important diagnostic feature of the hydrolytic process is the appearance of the C-4-bearing hydroxyl group, at about 175 ppm, well beyond the 145–155 ppm of the C-8-bearing one. Evidently the C-4 hydroxyl group, which can tautomerize to the pyridone structure, has considerable carbonyl character. This signal near 175 ppm developed on prolonged ageing of the samples dissolved in *DMF*-d_7 but did not develop in P*y*-d_5 The ^{1}H NMR spectra of the 4-hydroxy compounds also showed the proton at C-3 to be shifted to lower δ values and its coupling constant to the H-2 proton to be increased above the usual value in a pyridine ring (4–5 Hz) to 6.5–7.5 Hz. Also in these compounds C-3 had its chemical shift near 110 ppm or less instead of 125–130 ppm in the starting compounds.

This work was carried out primarily to understand what took place with 4-halo-8-quinolinols as a result of ageing in *DMSO*. In a classical textbook it is stated that polar solvents accelerated the hydrolysis of halogen at the 4 position of quinolines [5]. This is expected because 4-haloquinolines are vinylogous heteroanalogs of acid chlorides. 4-Chloro-8-quinolinol is stable to boiling in 76% sulfuric acid for five hours [6]. While this is a polar solvent with a significant concentration of the nucleophile H_2O, it is a protic solvent which inhibits the hydrolysis. Data reported in the present work show the accelerated hydrolysis in *DMSO* and *DMF* but not in pyridine. Pyridine is classified as a nonpolar aprotic solvent while *DMSO* and *DMF* are listed as dipolar aprotic solvents [7]. Hence, it is this distinction as to solvent type which seems to explain these results.

Although we have no detailed experimental evidence to support it, a mechanism based on literature analogies is presented in Scheme 1. It has been shown that



Scheme 1

alkoxydimethylsulfonium salts are intermediates in certain solvolytic reactions in *DMSO* [8]. Such a salt is proposed as an intermediate in the formation of a bromoalcohol from stilbene by reaction with *N*-bromosuccinimide in *DMSO*. Upon quenching with water a secondary alcohol is formed [9]. Using this model, we believe that the hydrolysis of 4-halo-8-quinolinols in *DMSO* and *DMF* can follow a similar pathway. If the structures of *DMSO* and *DMF* are aligned it can be seen that the S=O and C=O groups might react similarly. Scheme 1 contains our proposed mechanism for the hydrolysis of 4-halo-8-quinolinols in *DMSO*. An analogous argument would apply to *DMF*. It should be noted that the oxygen introduced in the 4 position of the 4,8-quinolindiol is supplied by that of *DMSO* or *DMF* and these solvents are regenerated by reaction with water as was proven for halohydrin formation from stilbene in *DMSO* [10]. Hence, these solvents are catalysts for the hydrolysis.

Experimental

Samples of **1**–**4** were examined by ^{1}H and ^{13}C NMR spectroscopy at 300 and 75 MHz with a Bruker DPX-300 spectrometer using *DMSO-d*$_6$ or C_5D_5N (*Py*-d_5) or *DMF-d*$_7$ as solvent and *TMS* as internal standard. Spectra were rerun each day to follow the hydrolytic process as the samples absorbed water from the atmosphere.

5-Chloro-4,8-dihydroxyquinoline (**1a**, $C_9H_6ClNO_2$)

^{1}H NMR (300 MHz, *DMSO-d*$_6$): $\delta = 11.27$ (OH), 11.13 (OH), 7.74 (d, $J = 7.2$ Hz, H-2), 7.12 (d, $J = 8.30$ Hz, H-6) 7.03 (d, $J = 8.30$ Hz, H-7), 6.07 (d, H-3) ppm; ^{13}C NMR (75 MHz, *DMSO-d*$_6$): $\delta = 176.4$ (C-4), 145.7 (C-8), 137.9 (C-2), 132.7 (C-8a), 125.0 (C-6), 122.2 (C-5), 120.5 (C-4a), 113.9 (C-7), 111.0 (C-3) ppm; ^{1}H NMR (300 MHz, *Py*-d_5): $\delta = 7.95$ (d, $J = 7.3$ Hz, H-2), 7.28 (d, $J = 8.30$ Hz, H-6) 7.18 (d, $J = 8.30$ Hz, H-7), 6.57 (d, H-3) ppm; ^{13}C NMR (75 MHz, *Py*-d_5): $\delta = 178.0$ (C-4), 147.4 (C-8), 137.9′(C-2), 134.6 (C-8a), 125.8 (C-6), 123.2 (C-4a), 122.2 (C-5), 114.5 (C-7), 112.2 (C-3) ppm; HRMS (m/z): calcd for $C_9H_6{}^{35}ClNO_2$ 195.00871, found 195.00834.

5-Bromo-4,8-dihydroxyquinoline (**2a**, $C_9H_6BrNO_2$)

^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.73$ (d, $J = 6.58$ Hz, H-2), 7.78 (d, $J = 8.42$ Hz, H-6), 7.50 (d, H-7) 7.38 (d, H-3) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 173.1$ (C-4), 148.3 (C-8), 143.3 (C-2), 133.9 (C-6), 133.5 (C-8a), 120.8 (C-4a), 116.8 (C-3), 108.9 (C-7), 108.1 (C-5), ppm; HRMS (m/z): calcd for $C_9H_6{}^{79}BrNO_2$ 238.95819, found 238.95754.

3,5-Dibromo-4,8-dihydroxyquinoline (**2b**, $C_9H_5Br_2NO_2$)

^{1}H NMR (300 MHz, *DMSO-d*$_6$): $\delta = 11.68$ (OH), 11.24 (OH), 8.14 (s, H-2), 7.41 (d, $J = 8.18$ Hz, H-6) 6.98 (d, H-7) ppm; ^{13}C NMR (75 MHz, *DMSO-d*$_6$): $\delta = 170.2$ (C-4), 146.5 (C-8), 138.5 (C-2), 131.8 (C-8a), 129.8 (C-6), 121.2 (C-5), 114.7 (C-7), 106.9 (C-4a), 106.3 (C-3) ppm; HRMS (m/z): calcd for $C_9H_5{}^{79}Br_2NO_2$ 316.86870, found 316.86953.

5,7-Dichloro-4,8-dihydroxyquinoline (**3a**, $C_9H_5Cl_2NO_2$)

^{1}H NMR (300 MHz, *DMSO-d*$_6$): $\delta = 8.18$ (d, $J = 7.05$ Hz, H-2), 7.54 (s, H-6), 6.74 (d, H-3) ppm; $^{1}3C$ NMR (75 MHz, *DMSO-d*$_6$): $\delta = 173.5$ (C-4), 142.2 (C-8), 141.3 (C-2), 137.0 (C-8a), 134.2 (C-6),

121.3 (C-5), 120.9 (C-4a), 119.0 (C-7), 109.7 (C-3) ppm; ^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.57$ (d, $J = 6.93$ Hz, H-2), 7.62 (s, H-6), 7.30 (d, H-3) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 174.3$ (C-4), 149.9 (C-8), 143.7 (C-2), 135.0 (C-8a), 129.9 (C-6), 126.7 (C-5), 122.2 (C-4a), 118.3 (C-7), 109.85 (C-3) ppm; HRMS (m/z): calcd for $C_9H_5{}^{35}Cl_2NO_2$ 228.96973, found 228.97013.

5,7-Dibromo-4,8-dihydroxyquinoline (**4a**, $C_9H_5Br_2NO_2$)

^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.35$ (d, $J = 7.07$ Hz, H-2), 7.68 (s, H-6), 6.81 (d, H-3) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 174.5$ (C-4), 145.2 (C-8), 141.6 (C-2), 135.2 (C-8a), 133.7 (C-6), 122.2 (C-4a), 110.6 (C-3), 108.8 (C-5), 107.2 (C-7), ppm; HRMS (m/z): calcd for $C_9H_5{}^{79}Br_2NO_2$ 316.86870, found 316.86953.

3,5,7-Tribromo-4,8-dihydroxyquinoline (**4b**, $C_9H_4Br_3NO_2$)

^{1}H NMR (300 MHz, *DMSO-d*$_6$): $\delta = 8.15$ (s, H-2), 7.67 (s, H-6) ppm; ^{13}C NMR (75 MHz, *DMSO-d*$_6$): $\delta = 169.9$ (C-4), 143.6 (C-8), 138.8 (C-2), 133.6 (C-8a), 131.6 (C-6), 120.2 (C-4a), 111.1 (C-5), 109.0 (C-7), 106.8 (C-3) ppm; HRMS (m/z): calcd for $C_9H_4{}^{79}Br_3NO_2$ 394.77921, found 394.77917.

4,5-Dichloro-8-quinolinol **(1)**

Spectral data for this compound in *DMSO-d*$_6$ have been described previously [1]. ^{1}H NMR (300 MHz, *Py*-d$_5$): $\delta = 8.68$ (d, $J = 4.57$ Hz, H-2), 7.63 (d, $J = 8.47$ Hz, H-6), 7.55 (d, H-3), 7.35 (d, H-7) ppm; ^{13}C NMR (75 MHz, *Py*-d$_5$): $\delta = 154.7$ (C-8), 147.8 (C-2), 141.8 (C-4), 141.4 (C-8a), 132.4 (C-6), 125.9 (C-3), 124.0 (C-4a), 117.9 (C-5), 112.5 (C-7) ppm; ^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.82$ (d, $J = 4.60$ Hz, H-2), 7.71 (d, $J = 8.44$ Hz, H-6), 7.83 (d, H-3), 7.23 (d, H-7) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 154.2$ (C-8), 148.9 (C-2), 141.6 (C-4), 141.2 (C-8a), 132.7 (C-6), 126.7 (C-4a), 123.9 (C-3), 117.9 (C-5), 112.5 (C-7) ppm.

4,5-Dibromo-8-quinolinol **(2)**

^{1}H NMR data for this compound in *DMSO-d*$_6$ have been described previously [2]. ^{13}C NMR (75 MHz, *DMSO-d*$_6$): $\delta = 154.0$ (C-8), 147.6 (C-2), 140.5 (C-8a), 130.4 (C-4), 136.6 (C-6), 130.1 (C-3), 124.6 (C-4a), 112.7 (C-7), 104.8 (C-5) ppm; ^{1}H NMR (300 MHz, *CDCl*$_3$): $\delta = 8.46$ (d, $J = 4.60$, H-2), 7.88 (d, $J = 8.73$ Hz, H-6), 7.88 (d, H-3), 7.06 (d, H-7) ppm; ^{13}C NMR (75 MHz, *CDCl*$_3$): $\delta = 152.6$ (C-8), 146.7 (C-2), 140.3 (C-8a), 136.1 (C-6), 132.4 (C-4), 130.1 (C-3), 125.3 (C-4a), 111.2 (C-7), 106.7 (C-5) ppm; ^{1}H NMR (300 MHz, *Py*-d$_5$): $\delta = 8.53$ (d, $J = 4.54$, H-2), 7.92 (d, $J = 8.42$ Hz, H-6), 7.86 (d, H-3), 7.25 (d, H-7) ppm; ^{13}C NMR (75 MHz, *Py*-d$_5$): $\delta = 155.6$ (C-8), 147.4 (C-2), 141.7 (C-8a), 136.7 (C-4), 131.8 (C-6), 130.3 (C-3), 125.7 (C-4a), 113.1 (C-5), 106.0 (C-7) ppm; ^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.82$ (d, $J = 4.61$ Hz, H-2), 7.83 (d, H-3), 7.71 (d, $J = 8.45$ Hz, H-6), 7.23 (d, H-7) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 154.6$ (C-8), 148.2 (C-2), 140.9 (C-8a), 137.2 (C-4), 132.3 (C-6), 131.8 (C-3), 125.7 (C-4a), 113.3 (C-5), 106.0 (C-7) ppm.

4,5,7-Trichloro-8-quinolinol **(3)**

NMR spectral data for this compound in *DMSO-d*$_6$ have been described previously [3]. ^{1}H NMR (300 MHz, *Py*-d$_5$): $\delta = 8.67$ (d, $J = 4.47$ Hz, H-2), 7.78 (s, H-6), 7.53 (d, H-3) ppm; ^{13}C NMR (75 MHz, Py-d$_5$): $\delta = 154.6$ (C-8), 149.1 (C-2), 142.0 (C-4), 141.6 (C-8a), 132.1 (C-6), 125.7 (C-3), 118.0 (C-4a), 117.4 (C-5), 112.5 (C-7) ppm; ^{1}H NMR (300 MHz, *DMF-d*$_7$): $\delta = 8.86$ (d, $J = 4.64$ Hz, H-2), 7.85 (d, H-3), 7.81 (s, H-6) ppm; ^{13}C NMR (75 MHz, *DMF-d*$_7$): $\delta = 150.5$ (C-8), 149.9 (C-2), 141.6 (C-4), 141.2 (C8a), 132.4 (C-6), 126.7 (C-3), 122.8 (C-4a), 118.3 (C-5), 116.8 (C-7) ppm.

4,5,7-Tribromo-8-quinolinol **(4)**

Spectral data for this compound in *DMSO-d_6* have been described previously [3]. ^{1}H NMR (300 MHz, *Py*-d_5): $\delta = 8.52$ (d, $J = 4.47$ Hz, H-2), 8.26 (s, H-6), 7.87 (d, H-3) ppm; ^{13}C NMR (75 MHz, *Py*-d_5): $\delta = 153.4$ (C-8), 148.7 (C-2), 141.5 (C-8a), 138.8 (C-6), 132.0 (C-4), 130.3 (C-3), 124.9 (C-4a), 106.8 (C-5), 106.2 (C-7) ppm; ^{1}H NMR (300 MHz, *DMF-d_7*): $\delta = 8.71$ (d, $J = 4.59$ Hz, H-2), 8.14 (d, H-3), 8.18 (s, H-6), ppm; ^{13}C NMR (75 MHz, *DMF-d_7*): $\delta = 152.6$ (C-8), 149.4 (C-2), 141.1 (C-8a), 138.7 (C-6), 131.9 (C-4), 131.3 (C-3), 124.9 (C-4a), 106.4 (C-5), 105.9 (C-7) ppm.

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