Monatshefte für Chemie 132, 1075–1080 (2001)

**Monatshefte für Chemie**
**Chemical Monthly**


# Preparation and Fungitoxicity of Some Trichloro-, Tribromo-, Tetrachloro-, and Tetrabromo-8-Quinolinols

**Herman Gershon**[1,2,*], **Donald D. Clarke**[1], and **Muriel Gershon**[2]

[1] Department of Chemistry, Fordham University, Bronx, NY 10458-9993 USA
[2] New York Botanical Garden, Bronx, NY 10458-9993 USA

**Summary.** 3,5,6-, 3,5,7-, 4,5,7-, and 5,6,7-trichloro- and -tribromo-8-quinolinols as well as 3,5,6,7-tetrachloro- and -tetrabromo-8-quinolinols were prepared and tested against six fungi (*Aspergillus niger*, *Aspergillus oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes*) in *Sabouraud* dextrose broth. The compounds strongly inhibit five fungi but not *M. cirinelloides*. They are less active than the related dichloro-8-quinolinols which is attributed to steric hindrance.

**Keywords.** Trichloro-8-quinolinols; Tribromo-8-quinolinols; Tetrachloro-8-quinolinols; Tetrabromo-8-quinolinols; Antifungal activity.

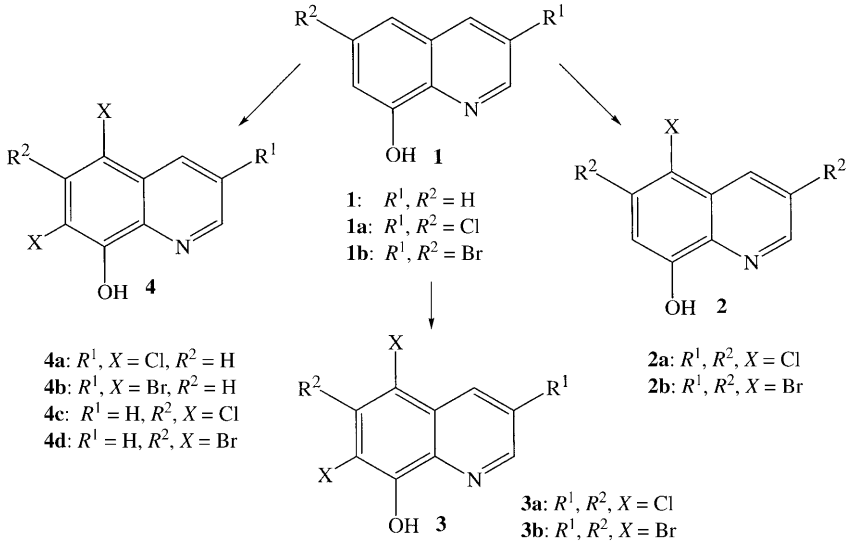
## Introduction

It has been shown previously that the antifungal activity of monochloro- and monobromo-8-quinolinols, with the exception of the 2-substituted analogues, exceeds that of 8-quinolinol [1]. This has been attributed to intramolecular synergism [2]. The enhanced activity of the dihalo-8-quinolinols over the monohalo analogues has been explained similarly by intramolecular synergism [2–4]. It seemed of interest to determine if further enhancement of toxicity would result from tri- and tetrasubstitution.

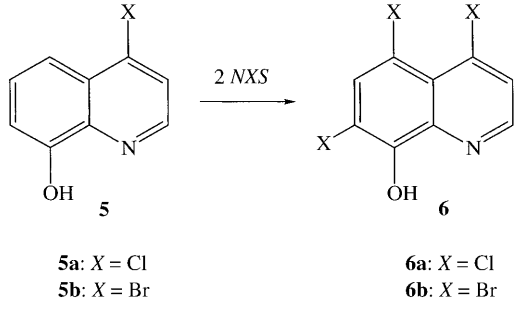
## Results and Discussion

The 3,5,6-Trichloro- and 3,5,6-tribromo-8-quinolinols **2a**,**b** were prepared from the respective 3,6-dihalo-8-quinolinols **1a**,**b** [5] by reaction with one equivalent of N-chloro-succinimide (*NCS*) or N-bromosuccinimide (*NBS*) in 93% sulfuric acid at ambient temperature. The 3,5,6,7-tetrahalo-8-quinolinols **3a**,**b** were obtained by halogenation with two equivalents of N-halosuccinimide (*NXS*) in acetic acid. For the preparation of 3,5,7- (**4a**,**b**) and 5,6,7-trihalo-8-quinolinols (**4c**,**d**), the respective monohalo-8-quinolinol [6] was reacted with two equivalents of *NXS* in glacial

* Corresponding author. E-mail: clarke@fordham.edu




**Scheme 1**




**Scheme 2**

acetic acid at ambient temperature (Scheme 1). The preparation of the 4,5,7-trihalo-8-quinolinols **6a**,**b** from the respective monohalo-8-quinolinols **5a**,**b** [6] was achieved in a manner similar to that employed for **4a–d** (Scheme 2). Compounds **4a** and **4c** were obtained previously as by-products from the chlorination of the respective monochloro-5-sulfonic acids [3]. $^{1}H$ and $^{13}C$ NMR data characterize the new compounds and are reported in the experimental section. Whereas all compounds reported here are stable indefinitely in the solid state, **6a**,**b** and **7a**,**b** were unstable in *DMSO* solution; thus, spectra and antifungal activity had to be measured using freshly prepared solutions in these cases.

Antifungal data for the ten tri- and tetrahalo-8-quinolinols are shown in Table 1. In general, the compounds were highly fungitoxic. Except for *M. cirinelloides*, almost all of them were more active than 8-quinolinol (**1**) against the other five fungi. Where comparisons are possible, all chloro derivatives were more inhibitory than the corresponding bromo analogues, which is consistent with what has been reported for the dichloro- and dibromo-8-quinolinols [4]. Comparisons can be made of the activity of the compounds against *A. niger* and *T. viride*, since the minimal

**Table 1.** Antifungal activity of trichloro-, tribromo-, tetrachloro-, and tetrabromo-8-quinolinols in *Sabouraud* dextrose broth at 28°C in shake culture after six days

| | Minimal Inhibitory Concentrations/mmol · dm$^{-3}$ (μg · cm$^{-3}$) | | |
|---|---|---|---|
| | *A. niger* | *A. oryzae* | *M. verrucaria* |
| **2a** | 0.012 (3) | < 0.0040 (< 1)[a] | < 0.0040 (< 1) |
| **4a**[b] | < 0.0040 (< 1) | < 0.0040 (< 1) | < 0.0040 (< 1) |
| **6a**[c] | 0.025 (5) | < 0.0040 (< 1) | < 0.0040 (< 1) |
| **4c** | 0.0080 (2) | < 0.0040 (< 1) | < 0.0040 (< 1) |
| **3a** | < 0.0035 (< 1) | < 0.0035 (< 1) | < 0.0035 (< 1) |
| **2b** | > 0.26 (> 100) | < 0.0026 (< 1) | < 0.0026 (< 1) |
| **4b** | 0.0052 (2) | < 0.0026 (< 1) | < 0.0026 (< 1) |
| **6b**[c] | 0.026 (10) | 0.0052 (2) | < 0.0026 (< 1) |
| **4d** | 0.018 (7) | < 0.0026 (< 1) | < 0.0026 (< 1) |
| **3b** | > 0.22 (> 100) | < 0.0022 (< 1) | < 0.0022 (< 1) |
| **1**[d] | 0.14 (20) | 0.12 (18) | 0.034 (5) |
| | *T. viride* | *M. cirinelloides* | *T. mentagrophytes* |
| **2a** | 0.025 (5) | > 0.40 (> 100) | < 0.0040 (< 1) |
| **4a**[b] | < 0.0040 (< 1) | > 0.40 (> 100) | < 0.0040 (< 1) |
| **6a**[c] | 0.025 (5) | > 0.40 (> 100) | < 0.0040 (< 1) |
| **4c** | 0.028 (7) | > 0.40 (> 100) | < 0.0040 (< 1) |
| **3a** | 0.018 (5) | > 0.35 (> 100) | < 0.0035 (< 1) |
| **2b** | > 0.26 (> 100) | > 0.26 (> 100) | < 0.0026 (< 1) |
| **4b** | < 0.0026 (< 1) | > 0.26 (> 100) | < 0.0026 (< 1) |
| **6b**[c] | 0.026 (10) | > 0.26 (> 100) | < 0.0026 (< 1) |
| **4d** | 0.079 (30) | > 0.26 (> 100) | < 0.0026 (< 1) |
| **3b** | > 0.22 (> 100) | > 0.22 (> 100) | < 0.0026 (< 1) |
| **1**[d] | 0.14 (20) | 0.17 (24) | 0.041 (6) |

[a] The symbol < indicates below 1 μg/cm$^3$ (the lowest level tested), > indicates above 100 μg/cm$^3$ (the highest level tested); *MIC*s from 1–10 were obtained in increments of 1 and from 10–100 in increments of 10; [b]Ref. [3]; [c]for reproducible results, fresh solutions had to be prepared for each test (cf. text); [d]data taken from Ref. [6].

inhibitory concentrations were above 1 μg/cm$^3$, and relationships might be determined. When the fungitoxicity of the dichloro-8-quinolinols [3] is compared with that of the trichloro compounds containing substituents in positions corresponding to those in the dichloro-8-quinolinols, the dichloro compounds were almost always more active than the trichloro analogues. The good activity of 3,5,6-trichloro-8-quinolinol (**2a**) and its 3,5,6,7-tetrachloro analogue **3a** should be noted as compared with the corresponding tri- (**2b**) and tetrabromo (**3b**) analogues which do not inhibit the fungi below 100 μg/cm$^3$, the highest level tested. 3,6- and 5,7-dichloro-8-quinolinols and their dibromo analogues form synergistic mixtures [2]. In view of prior results concerning intramolecular synergism in mono- and dihalo-8-quinolinols it might have been expected that the tri- and tetrahalo-8-quinolinols would owe their activities to intramolecular synergism. Since this was not observed, steric hindrance might be an explanation for the diminished fungitoxicity of the latter groups of 8-quinolinols. If this is the case, it would suggest that position, size,

and number of substituents will have to be considered in developing compounds showing intramolecular synergism.

## Experimental

*Antifungal testing*

Antifungal testing was performed in *Sabouraud* dextrose broth (Difco) according to Refs. [7–10]. The fungi employed included *Aspergillus niger* (ATCC 1004), *Aspergillus oryzae* (ATCC 1011), *Myrothecium verrucaria* (ATCC 9095), *Trichoderma viride* (ATCC 8678), *Mucor cirinelloides* (ATCC 7941), and *Trichophyton mentagrophytes* (ATCC 9129).

*Compounds*

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Purity and identity of samples were established by $^{1}H$ and $^{13}C$ NMR spectroscopy at 300 and 75 MHz with a Bruker DPX-300 spectrometer using *DMSO*-$d_6$ as solvent and *TMS* as internal standard. Elemental analysis matched the calculated values satisfactorily for **2a**, **3a**, **6a** (C, H, Cl, N), **2b**, **3b**, **6b** (C, H, Br, N), **7a** (C, H, Cl, N, S), and **7b** (C, H, Br, N, S).

*3,5,6-Trichloro-8-quinolinol* (**2a**; $C_9H_4Cl_3NO$)

**1a** [5] (1.22 g, 0.006 mol) dissolved in 25 $cm^3$ of 93% $H_2SO_4$ was reacted with *NCS* (0.88 g, 0.0066 mol) under stirring at ambient temperature overnight. The solution was poured into 300 $cm^3$ of deionized $H_2O$ and stirred for 10 min. **2a** was obtained by filtration, washing with deionized $H_2O$, and drying at 50°C.

Yield 1.4 g (93%); m.p.: 207–208°C ($CH_3CN$); $^{1}H$ NMR: $\delta = 8.91$ (d, $J_{24} = 1.94$ Hz, H-2), 8.50 (d, H-4), 7.27 (s, H-7), 11.01 (s, OH) ppm; $^{13}C$ NMR: $\delta = 153.70$ (C-8), 147.69 (C-2), 136.13 (C-8a), 131.81 (C-6), 130.73 (C-4), 130.48 (C-3), 127.11 (C-4a), 115.53 (C-5), 113.19 (C-7) ppm.

*3,5,6-Tribromo-8-quinolinol* (**2b**; $C_9H_4CBr_3NO$)

**2b** was prepared from **1b** [5] by reaction with *NBS* in the same manner as **2a** was obtained from **1a**.

Yield: 90% (0.002 mol run); m.p.: 235–236°C (EtOH, 2x); $^{1}H$ NMR: $\delta = 8.94$ (d, $J_{24} = 1.53$ Hz, H-2), 8.59 (d, H-4), 7.44 (s, H-7), 3.63 (bs, OH and $H_2O$) ppm; $^{13}C$ NMR: $\delta = 154.10$ (C-8), 149.47 (C-2), 136.76 (C-4), 136.55 (C-8a), 125.40 (C-3), 120.02 (C-6), 125.16 (C-4a), 116.40 (C-5), 109.67 (C-7) ppm.

*3,5,7-Trichloro-8-quinolinol* (**4a**; $C_9H_4Cl_3NO$)

Preparation and NMR spectra of **4a** have been described previously [3].

*3,5,7-Tribromo-8-quinolinol* (**4b**; $C_9H_4Br_3NO$)

To a solution of 3-bromo-8-quinolinol [6] (1.5 g, 0.0067 mol) in 150 $cm^3$ of acetic acid at 60°C, *NBS* (2.6 g, 0.015 mol) was added, and the mixture was stirred for 5 days. The solution was poured into 500 $cm^3$ of deionized $H_2O$ with stirring. The product was obtained by filtration, washing with deionized $H_2O$, and air drying.

Yield: 2.7 g (98%); m.p.: 170°C ($CH_3CN$; Ref. [11]: m.p.: 170°C, yield not given); $^1H$ NMR: $\delta = 8.80$ (d, $J_{24} = 2.20$ Hz, H-2), 8.50 (d, H-4), 8.05 (s, H-6), 11.80 (s, OH) ppm; $^{13}C$ NMR: $\delta = 154.61$ (C-8), 149.98 (C-2), 137.32 (C-4), 137.07 (C-8a), 129.76 (C-6), 125.88 (C-4a), 120.50 (C-3), 116.91 (C-5), 110.09 (C-7) ppm.

*4,5,7-Trichloro-8-quinolinol* (**6a**; $C_9H_4Cl_3NO$)

**6a** was prepared from 4-chloro-8-quinolinol [6] (2.0 g, 0.011 mol) in 200 $cm^3$ of acetic acid by stirring for 6 days at room temperature with *NCS* (3.2 g, 0.024 mol). The solution was diluted with 1000 $cm^3$ of deionized $H_2O$, and the product was recovered by filtration, washing with deionized $H_2O$, and drying at 50°C.

Yield: 3.1 g (98%); m.p.: 154°C ($CH_3CN$); $^1H$ NMR: $\delta = 8.82$ (d, $J_{23} = 4.68$ Hz, H-2), 7.84 (d, H-3), 7.82 (s, H-6), 11.02 (s, OH) ppm; $^{13}C$ NMR: $\delta = 149.48$ (C-8), 148.92 (C-2), 140.32 (C-4), 140.64 (C-8a), 131.51 (C-6), 125.84 (C-3), 121.72 (C-4a), 116.94 (C-5), 116.11 (C-7) ppm.

*4,5,7-Tribromo-8-quinolinol* (**6b**; $C_9H_4Br_3NO$)

**6b** was prepared from 4-bromo-8-quinolinol [6] in the same manner as **6a** was obtained from 4-chloro-8-quinolinol.

Yield: 1.2 g (70%); m.p.: 150–151°C ($CH_3CN$); $^1H$ NMR: $\delta = 8.67$ (d, $J_{23} = 4.43$ Hz, H-2), 8.12 (d, H-3), 8.15 (s, H-6), 11.06 (s, OH) ppm; $^{13}C$ NMR: 151.46 (C-8), 148.43 (C-2), 140.10 (C-8a), 137.70 (C-6), 130.91 (C-4), 130.29 (C-3), 123.79 (C-4a), 105.59 (C-5), 105.39 (C-7) ppm.

*5,6,7-Trichloro-8-quinolinol* (**4c**; $C_9H_4Cl_3NO$)

**4c** was prepared from 6-chloro-8-quinolinol [6] as **6a** was obtained from 4-chloro-8-quinolinol.

Yield: 99% (0.011 mol run); m.p.: 213–214°C ($CH_3CN$; Ref. [12]: m.p.: 213–214°C, Ref. [13]: m.p.: 220–225°C, yields not given); NMR data: see Ref. [3].

*5,6,7-Tribromo-8-quinolinol* (**4d**; $C_9H_4Br_3NO$)

**4d** was prepared from 6-bromo-8-quinolinol [6] as **6a** was obtained from 6-chloro-8-quinolinol.

Yield: 97% (0.009 mol run); m.p.: 196°C ($CH_3CN$; Ref. [11]: m.p.: 192°C, yield not given); $^1H$ NMR: $\delta = 8.98$ (dd, $J_{23} = 4.11$ Hz, $J_{24} < 1$ Hz, H-2), 8.63 (dd, H-4), 11.48 (s, OH) ppm; $^{13}C$ NMR: $\delta = 152.16$ (C-8), 149.85 (C-2), 137.67 (C-8a), 136.67 (C-4), 127.14 (C-4a), 127.01 (C-6), 124.57 (C-3), 112.00 (C-5), 108.63 (C-7) ppm.

*3,5,6,7-Tetrachloro-8-quinolinol* (**3a**; $C_9H_3Cl_4NO$)

**1a** [5] (1.1 g, 0.005 mol) was dissolved in acetic acid (100 $cm^3$) to which *NCS* was added (1.4 g, 0.0105 mol); the mixture was stirred overnight at 40°C. The solution was diluted with 500 $cm^3$ of deionized $H_2O$. **3a** was removed by filtration, washed with deionized $H_2O$, and dried at 50°C.

Yield: 1.39 g (98%); m.p.: 159–160°C ($CH_3CN$); $^1H$ NMR: $\delta = 8.91$ (d, $J_{24} = 2.22$ Hz, H-2), 8.39 (d, H-4), 11.68 (s, OH) ppm; $^{13}C$ NMR: $\delta = 150.83$ (C-8), 148.78 (C-2), 135.41 (C-8a), 131.38 (C-6), 131.19 (C-4), 130.87 (C-3), 125.18 (C-4a), 117.19 (C-5), 116.55 (C-7) ppm.

*3,5,6,7-Tetrabromo-8-quinolinol* (**3b**; $C_9H_3Br_4NO$)

**3b** was prepared from **1b** [5] by bromination with *NBS* in the same manner as **3a** was obtained from **1a**.

Yield: 93% (0.0033 mol run); m.p.: 199–201°C ($CH_3CN$); $^1H$ NMR: $\delta = 8.96$ (d, $J_{24} = 2.04$ Hz, H-2), 8.58 (d, H-4), 11.69 (s, OH) ppm; $^{13}C$ NMR: $\delta = 152.19$ (C-8), 150.16 (C-2), 137.46 (C-4), 136.35 (C-8a), 128.65 (C-4a), 127.57 (C-6), 120.11 (C-3), 110.62 (C-5), 109.64 (C-7) ppm.

*3,6-Dichloro-8-quinolinol-5-sulfonic acid* (**7a**; $C_9H_5Cl_2NO_4S$)

**1a** [5] (2.0 g, 0.009 mol) was added to 14 $cm^3$ of 20% oleum, and the mixture was heated with stirring to 100°C for 15 min. It was refrigerated overnight and poured into an ice-$H_2O$ slurry with stirring. The crystallized material was separated by filtration, washed with $H_2O$, boiled twice with acetone, and filtered again.

Yield: 2.0 g (73%); m.p.: 258–259°C (*DMSO* aq.); $^1H$ NMR: $\delta = 9.83$ (d, H-4), 8.88 (d, $J_{24} = 2.22$ Hz, H-2), 7.98 (s, OH), 7.10 (s, H-7) ppm; $^{13}C$ NMR: $\delta = 153.50$ (C-8), 145.83 (C-2), 135.70 (C-4), 134.76 (C-8a), 132.06 (C-5), 130.90 (C-6), 128.61 (C-3), 127.70 (C-4a), 114.50 (C-7) ppm.

*3,6-Bromo-8-quinolinol-5-sulfonic acid* (**7b**; $C_9H_5Br_2NO_4S$)

**7b** was prepared from **1b** [6] in the same manner as the above dichloro analogue.

Yield: 68% (0.006 mol run); m.p.: 257–258°C (aqueous *DMSO*); $^1H$ NMR: $\delta = 8.96$ (d, $J_{24} = 1.90$ Hz, H-2), 10.01 (d, H-4), 8.16 (s, OH), 7.20 (s, H-7) ppm; $^{13}C$ NMR: $\delta = 155.50$ (C-8), 148.83 (C-2), 137.10 (C-4), 137.9 (C-8a), 136.0 (C-5), 128.61 (C-3), 126.0 (C-4a), 118.6 (C-6), 116.6 (C-7) ppm.

## Acknowledgements

Partial support for this work was provided by the National Science Foundation's Division of Undergraduate Education through grant DUE #9650684.

## References

[1] Gershon H, Clarke DD, Gershon M (1994) Monatsh Chem **125**: 51
[2] Gershon H, Gershon M (1995) Monatsh Chem **126**: 1303
[3] Gershon H, Clarke DD, Gershon M (1999) Monatsh Chem **130**: 653
[4] Gershon H, Clarke DD, McMahon JJ, Gershon M (2001) Monatsh Chem **132**: 833
[5] Gershon H, Clarke DD, Gershon M (1994) Monatsh Chem **125**: 723
[6] Gershon H, Clarke DD (1991) Monatsh Chem **122**: 935
[7] Gershon H, Shanks L (1981) Can J Microbiol **27**: 612
[8] Gershon H, Grefig AT, Cady DJ (1985) Can J Microbiol **31**: 707
[9] Gershon H, Clarke DD, Gershon M (1989) J Pharm Sci **78**: 975
[10] Gershon H, Clarke DD, Gershon M (1993) Monatsh Chem **124**: 367
[11] Irving H, Pinnington AR (1957) J Chem Soc 290
[12] Hebenbrand A (1888) Chem Ber **21**: 2977
[13] Burckhalter JH, Stephens VC, Scarborough HC, Brinigar WS, Edgerton WH (1954) J Am Chem Soc **76**: 4902

*Received April 3, 2001. Accepted April 10, 2001*