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Preparation and Fungitoxicity of 3,6-Dichloro- and 3,6-Dibromo-8-Quinolinols

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Summary. 3,6-Dichloro- and 3,6-dibromo-8-quinolinols were prepared by direct halogenation of 8-nitroquinoline by N-halosuccinimide in acetic acid or by halogenation of the corresponding 6-halo-8-nitroquinoline prepared via a *Skraup* reaction. The nitro group was reduced to amino and the amine was hydrolyzed to the phenol in 70% sulfuric acid at 220 °C. The fungitoxicity of 3,6-dichloro- and 3,6-dibromo-8-quinolinols, as well as intermediates in their preparation, against *Aspergillus niger*, *Aspergillus oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, and *Mucor cirinelloides* was determined. 3,6-dichloro-8-quinolinol is the most fungitoxic analogue of this class of compounds observed to date.

Keywords. 3,6-dichloro-8-nitroquinoline; 3,6-dibromo-8-nitroquinoline; 8-amino-3,6-dichloroquinoline; 8-amino-3,6-dibromoquinoline; 3,6-dichloro-8-quinolinol; 3,6-dibromo-8-quinolinol; ^{1}H NMR spectra.

Herstellung und Fungitoxizität von 3,6-Dichlor- und 3,6-Dibrom-8-chinolinen

Zusammenfassung. 3,6-Dichlor- und 3,6-Dibrom-8-chinoline wurden durch direkte Halogenierung von 8-Nitrochinolin mit N-Halogensuccinimid in Essigsäure oder durch Halogenierung der entsprechenden nach *Skraup* synthetisierten 6-Halogen-8-nitrochinoline hergestellt. Die Nitrogruppe wurde zum Amin reduziert und die Aminofunktion in 70% iger Schwefelsäure bei 220 °C zum Phenol hydrolysiert. Die Fungitoxizität der 3,6-Dichlor- und 3,6-Dibrom-8-chinoline und jene der bei ihrer Herstellung auftretenden Zwischenstufen gegen *Aspergillus niger*, *Aspergillus oryzae*, *Myrothecium verrucaria*, *Trichoderma viride* und *Mucor cirinelloides* wurde bestimmt. 3,6-Dichlor-8-chinolin ist der derzeit stärkste bekannte fungitoxische Vertreter dieser Substanzklasse.

Introduction

In continuation of our studies of the antifungal activity of 8-quinolinol, its halogenated analogues, and their copper(II) chelates [1–12], we found it of interest to prepare, characterize and study the fungitoxic activity of 3,6-dichloro and 3,6-dibromo-8-quinolinols. These compounds were not described previously.

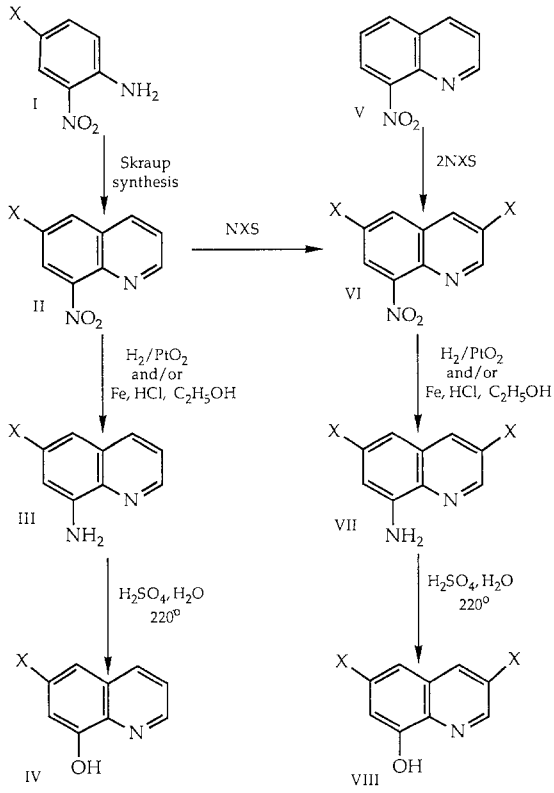
Results and Discussion

The 3,6-dihalo-8-quinolinols could be prepared by direct dihalogenation of 8-nitroquinoline with the corresponding N-halosuccinimide (*NXS*) in acetic acid,

followed by reduction of the nitro group to the amine either by hydrogenation over platinum oxide or by iron and hydrochloric acid in 95% ethanol. Hydrolysis of the amino group to the hydroxyl function was carried out in 70% aqueous sulfuric acid (w/w) at 220 °C in a sealed vessel, as was previously reported for 3-chloro and 3-bromo-8-quinolinols [11]. Alternatively, the 6-halo-8-nitroquinolines were prepared from the corresponding 4-halo-2-nitroanilines in high yield by a modification of the *Skraup* reaction [5, 13]. The second halogen atom could be added by means of *NXS* in hot acetic acid. Reduction of nitro compounds and hydrolysis of amines were carried out as above.

The preparation of 4-bromo-2-nitroaniline was carried out by direct bromination of 2-nitroaniline with *NBS* in acetic acid, as compared with bromination of 2-nitroacetanilide with elemental bromine followed by hydrolysis of the acetamido group. The *Skraup* reactions were based on the modification of *Palmer* [13] as further employed by *Gershon* et al. [11] in which the use of arsenic compounds as catalysts was eliminated. *m*-Nitrobenzenesulfonic acid sodium salt was used as the reaction promoter. The reactions are summarized in Scheme 1 and the ^{1}H NMR data obtained to characterize these compounds are listed in Table 1.

Since compounds from the present work and those previously reported [11] along with some of the commercially available intermediates used in these studies were available, we tested them for antifungal activity in *Sabouraud* dextrose broth



I - IV, VI - VIII a, X = Cl; I - IV, VI - VIII b, X = Br

Scheme 1

Table 1. ^{1}H NMR spectra of 3-, 6-, and 3,6-chloro- and bromo-, 8-nitro-, 8-amino-, and 8-hydroxyquinolinols

Chemical Shifts (δ), ppm[a].													
	Proton No.							Coupling Constant (Hz)					
Compound	2	3	4	5	6	7	O or N	J_{23}	J_{24}	J_{34}	J_{56}	J_{57}	J_{67}
8-NO_2-*Q*[b]	9.08(q)	7.81(q)	8.60(q)	8.27(q)	7.72(q)	8.35(q)	–	4.1	1.7	8.2	8	1.4	8
3-Cl-8-NO_2-*Q*[c]	9.05(d)	–	8.75(d)	8.25(q)	7.86(q)	8.33(q)	–	–	3	–	7	1.5	8
6-Cl-8-NO_2-*Q*	9.08(q)	7.80(q)	8.55(q)	8.44(d)	–	8.49(d)	–	4.1	1.7	8.5	–	2.2	–
3,6-Cl_2-8-NO_2-*Q*	9.03(d)	–	8.66(d)	8.34(d)	–	8.50(d)	–	–	2.3	–	–	2.2	–
3-Br-8-NO_2-*Q*[c]	9.25(d)	–	9.03(d)	8.39(q)	7.94(q)	8.46(q)	–	–	2	–	7	1.5	8
6-Br-8-NO_2-*Q*	9.08(q)	7.79(q)	8.55(q)	8.60(s)	–	8.60(s)	–	4.3	1.7	8.6	–	–	–
3,6-Br_2-8-NO_2-*Q*	9.12(d)	–	8.86(d)	8.56(d)	–	8.62(d)	–	–	2.3	–	–	2.1	–
8-NH_2-*Q*	8.74(q)	7.44(q)	8.17(q)	7.07(q)	7.29(q)	6.92(q)	6.1(s)	4.1	1.9	8.2	8.2	1.6	7.4
3-Cl-8NH_2-*Q*[c]	8.68(d)	–	8.34(d)	7.06(q)	7.37(q)	6.86(q)	6.02(s)	–	2.5	–	8	?	7
6-Cl-8NH_2-*Q*	8.74(q)	7.50(q)	8.15(q)	7.11(d)	–	6.80(d)	6.30(s)	4.1	1.7	8.2	–	2.2	–
3,6-Cl_2-8-NH_2-*Q*	8.67(d)	–	8.33(d)	7.08(d)	–	6.84(d)	6.37(s)	–	2.5	–	–	2.2	–
3-Br-8NH_2-*Q*[c]	8.85(d)	–	8.57(d)	7.13(q)	7.46(q)	7.06(q)	6.10(s)	–	2.0	–	8.0	1.5	7.0
6-Br-8NH_2-*Q*	8.74(q)	7.50(q)	8.15(q)	7.26(d)	–	6.47(d)	6.26(s)	4.1	1.4	8.2	–	2.1	–
3,6-Br_2-8-NH_2-*Q*	8.75(d)	–	8.47(d)	7.22(d)	–	7.00(d)	6.32(s)	–	2.2	–	–	2.2	–
8-OH-*Q*[c]	8.91(q)	7.57(q)	8.36(q)	7.48(q)	7.46(q)	7.22(q)	9.90(s)	4	1.5	8.5	8.1	1.1	7.8
3-Cl-8-OH-*Q*[c]	8.80(d)	–	8.50(d)	7.41(q)	7.53(q)	7.19(q)	10.1(s)	–	2.3	–	8.0	1.5	7.0
6-Cl-8-OH-*Q*[c]	8.89(q)	7.61(q)	8.32(q)	7.53(d)	–	7.15(d)	9.50(s)	4.0	1.5	8.5	–	1.8	–
3,6-Cl_2-8-OH-*Q*	8.82(d)	–	8.46(d)	7.48(d)	–	7.18(d)	10.7(s)	–	2.2	–	2.2	–	
3-Br-8-OH-*Q*[c]	8.95(d)	–	8.67(d)	7.44(q)	7.54(q)	7.25(q)	10.2(s)	–	2.0	–	8.0	1.5	7.0
6-Br-8-OH-*Q*[c]	8.96(q)	7.63(q)	8.35(q)	7.71(d)	–	7.30(d)	10.2(s)	4.0	1.5	8.5	–	2.0	–
3,6-Br_2-8-OH-*Q*	8.89(d)	–	8.61(d)	7.63(d)	–	7.24(d)	10.7(s)	–	2.2	–	–	2.1	–

[a] Spectra taken in *DMSO*-d_6 with *TMS* as internal standard.
[b] Q = Quinoline
[c] Data taken from Ref. [11]

(Difco) according to published methods [7–9, 14]. Five fungi were employed which included *Aspergillus niger* (ATCC 1004), *Aspergillus oryzae* (ATCC 1101), *Myrothecium verrucaria* (ATCC 9095), *Trichoderma viride* (ATCC 8678), and *Mucor cirinelloides* (ATCC 7941). The results are shown in Table 2. With the exception of the 3,6-dihalo-8-quinolinols, the best of the compounds showed only moderate antifungal activity. 3,6-Dichloro-8-quinolinol was completely inhibitory to four fungi at under 1 μg/ml and for *M. cirinelloides* the minimum inhibitory concentration was 7 μg/ml. The dibromo analogue was also completely inhibitory to three fungi at under 1 μg/ml, at 3 μg/ml against *A. niger*, and curiously at between 100 and 1000 μg/ml against *M. cirinelloides*. It should be noted that 3,6-dichloro-8-quinolinol is the most fungitoxic of the 8-quinolinols tested under comparable conditions.

Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of samples was established by gas chromatography and by ^{1}H NMR spectroscopy at 90 MHz. Gas chromatography was performed on a Varian Aerograph Model 1400 gas chromatograph with a flame ionization detector to which was attached a Varian Model 20 recorder. The column employed was 5 feet × 1/8 inch o.d., packed with 10% SE-30 on ChromosorbW, and nitrogen was used as the carrier gas. ^{1}H NMR spectra were obtained with a JEOL JNM-FX90Q spectrometer using *DMSO-d_6* as the solvent and *TMS* at the internal standard. 2-Nitroaniline, 4-chloro-2-nitroaniline, 8-nitroquinoline and 8-aminoquinoline were purchased from Aldrich Chemical Company, Milwaukee, WI.

4-Bromo-2-nitroaniline (**Ib**)

To a solution of 2-nitroaniline (13.8 g, 0.1 mol) in acetic acid (155 ml) was added *NBS* (18.0 g, 0.101 mol) with stirring and slow heating to boiling over 1 h or until the starch iodide test was negative. The mixture was poured into 10 volumes of water and stirred for 15 min. The product was removed by filtration, washed with water, and air dried. Compound **Ib** was obtained in 20.6 g (95%) yield, m.p. 107 °C. Crystallization from acetonitrile raised the melting point to 111–112 °C. (Ref. [15] m.p. 111.5–112.5 °C, [16] m.p. 112–113 °C, no yields given).

6-Chloro-8-nitroquinoline (**IIa**)

To a solution of sulfuric acid (118 g) in 50 ml of water was added sodium *m*-nitrobenzenesulfonate (58.4 g, 0.213 mol), glycerol (52.8 ml) and 4-chloro-2-nitroaniline (34.5 g, 0.2 mol) with stirring and gentle warming. The mixture was kept under reflux for 4 h, after which it was allowed to cool below 100 °C and poured into 2 l of water. The product was obtained by filtration and air dried. The yield of crude material was 40 g (97%), m.p. 146–148 °C. A sample crystallized from a mixture of acetonitrile, water and decolorizing carbon (Darco G-60) melted at 160–161 °C. (Ref. [17] m.p. crude product 142–155 °C (92.5%), crystallized product, m.p. 158–159 °C).

6-Bromo-8-nitroquinoline (**IIb**)

The title compound was prepared from **Ib** in the same manner as **IIa** was obtained from **Ia**. The yield of crude product from a 0.38 *M* run was 70 g (74%), m.p. 149–150 °C. Crystallization from 95% alcohol raised the m.p. to 174–175 °C. (Ref. [18] crude yield 95%, m.p. of crystallized product, 170 °C; Ref. [19] m.p. 172–173 °C).

Table 2. Antifungal activity (μg/ml) of some 2-nitroanilines, 8-nitroquinolines, 8-aminoquinolines and 3,6-dichloro- and 3,6-dibromo-8-quinolinols in *Sabouraud* dextrose broth at 28 °C in shake culture after six days[a]

Compound	*A. niger*	*A. oryzae*	*M. verrucaria*	*T. viride*	*M. cirinilleoides*
2-Nitroaniline	10^3	10^3	10^3	10^3	10^3
4-Chloro-2-nitroaniline	10^3	10^3	10^2	10^2	10^3
4-Bromo-2-nitroaniline	10^3	10^3	10^2	10^2	10^3
8-Nitroquinoline	$>10^3$	10^3	10^2	10^3	10^3
3-Chloro-8-nitroquinoline[b]	$>10^3$	10^3	10^3	10^3	$>10^3$
3-Bromo-8-nitroquinoline[b]	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
6-Chloro-8-nitroquinoline	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
6-Bromo-8-nitroquinoline	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
3,6-Dichloro-8-nitroquinoline	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
3,6-Dibromo-8-nitroquinoline	$>10^3$	$>10^3$	10^3	10^3	10^3
8-Aminoquinoline	10^3	10^2	10^2	10^2	10^2
8-Amino-3-chloroquinoline[b]	10^3	10^2	10^2	10^2	10^2
8-Amino-3-bromoquinoline[b]	10^3	10^2	10^2	10^2	10^2
8-Amino-6-chloroquinoline	10^3	10^2	10^2	10^2	10^3
8-Amino-6-bromoquinoline	10^3	10^3	10^2	10^2	10^3
8-Amino-3,6-dichloroquinoline	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
8-Amino-3,6-dibromoquinoline	$>10^3$	$>10^3$	$>10^3$	$>10^3$	$>10^3$
3,6-dichloro-8-quinolinol	<1	<1	<1	<1	7
3,6-dibromo-8-quinolinol	3	<1	<1	<1	10^3

[a] Test levels: 10, 10^2, 10^3 μg/ml except for 3,6-dihalo-8-quinolinols which were tested to 1 μg/ml.

[b] Data taken from Ref. [14]

3,6-Dichloro-8-nitroquinoline (**VIa**)

To 110 ml of acetic acid containing **IIa** (10.5 g, 0.05 mol) at 110 °C was added *NCS* (7.4 g, 0.055 mol) in small portions over 1 h with stirring. The solution was heated to boiling and stirring was continued for 2 h. The reaction mixture was monitored by gas chromatography for the disappearance of 6-chloro-8-nitroquinoline. The mixture was poured into 500 ml of water, stirred for 1/2 h filtered to remove the product. After washing with water and air drying the crude material weighed 12 g (96%), m.p. 147–151 °C. Crystallization from 95% ethanol raised the melting point to 159–160 °C. (Ref. [20] m.p. 160–161 °C, yield 14%).

A mixture of **V** (8.7 g, 0.05 mol) and *NCS* (13.4 g, 0.1 mol) in 110 ml of acetic acid was stirred at ambient temperatures for 2 weeks. The course of the reaction was monitored by gas chromatography until **VIa** appeared as the major product. The reaction mixture was worked up as above, and the yield of crude product was 7.5 g (60%), m.p. 145–150 °C. After three crystallizations from 95% ethanol, the product melted at 159–160 °C.

3,6-Dibromo-8-nitroquinoline (**VIb**)

The title compound was prepared from **IIb** and *NBS* in acetic acid in the same manner as **VIa** was prepared. The yield of product was 56.8 g (95%), m.p. 172–174 °C from a 0.18 *M* run. Recrystallization from 95% ethanol raised the melting point to 179–180 °C. (Ref. [19] m.p. 179–180 °C, yield 14%).

To 150 ml of acetic acid were added 15.2 g (0.06 mol) of **V** and 32 g (0.18 mol) of *NBS* with stirring at ambient temperatures in the same manner as **VIa** was prepared from **V**. The material was transferred to 1.5 l of water and stirred for 1 h. The product was removed by filtration, washed with water and air dried. The yield of compound was 19.8 g (99%), m.p. 165–175 °C. Two crystallization from 95% ethanol brought the melting point to 179–180 °C.

8-Amino-6-chloroquinoline (**IIIa**)

6-Chloro-8-nitroquinoline (**IIa**) (10.5 g, 0.05 mol) dissolved in 50 ml of methanol was shaken in a Parr hydrogenator in the presence of 50 mg of platinum oxide under 3 atmospheres of hydrogen. After the theoretical amount of hydrogen was taken up, the catalyst was removed by filtration and the solvent removed under reduced pressure. The residue was obtained in 8.9 g yield (99%), m.p. 69–71 °C. Crystallization from 95% ethanol raised the melting point to 72 °C. (Ref. [17] m.p. 73 °C, yield 70%; Ref. [21] m.p. 70–71 °C, yield 50% from 4-chloro-2-nitroaniline).

A mixture of **IIa** (10.5 g, 0.05 mol), iron powder (10.5 g, 0.18 mol) and concentrated hydrochloric acid (1 ml) in 340 ml of 95% ethanol was heated under reflux for 3 h with stirring. The iron and its oxides were removed by filtration, and the filtrate was poured into 2 l of water and subjected to steam distillation. A yield of 7.8 g (87%) of product was obtained, m.p. 66–67 °C. Crystallization from 95% ethanol raised the melting point to 71–72 °C. Due to the solubility of **IIIa** in water, the mother liquor from the stream distillation was evaporated under a stream of air in order to recover a significant amount of product.

8-Amino-6-bromoquinoline (**IIIb**)

Compound **IIIb** was prepared from **IIb** by reduction with iron and hydrochloric acid in 95% ethanol in the same manner as **IIIa** was prepared from **IIa**. The yield of product from a 0.06 *M* run was 9.6 g (72%), m.p. 71–72 °C. A sample crystallized from 95% ethanol melted at 75–76 °C. (Ref. [21] m.p. 70–71 °C, yield 50% from 4-bromo-2-nitroaniline. Our yield from the same starting material was also 50%).

8-Amino-3,6-dichloroquinoline (**VIIa**)

Compound **VIa** was reduced in 95% ethanol in the presence of iron powder and hydrochloric acid in the same manner as **IIa** was reduced to **IIIa**. The yield of product from a 0.09 *M* run was 18.7 g (95%), m.p. 114–115 °C. Steam distillation followed by crystallization from 95% ethanol raised the melting point to 119 °C. Anal.: calcd. for $C_9H_6Cl_2N_2$: C 50.74, H 2.84, Cl 32.28, N 13.15; found: C 50.55, H 2.88, Cl 32.63, N 12.87.

8-Amino-3,6-dibromoquinoline (**VIIb**)

Compound **VIIb** was prepared from **VIb** in the same manner as **VIIa** was obtained from **VIa**. The yield of product from a 0.06 *M* run was 94%, m.p. 119–120 °C. (Ref. [19] m.p. 119–120 °C, yield 80–90%).

6-Chloro-8-quinolinol (**IVa**)

Compound **IIIa** (3.0 g, 0.017 mol) was suspended in a mixture of sulfuric acid (10.3 g) and water (8.1 ml) in a glass tube sealed in a stainless steel pressure vessel containing a small amount of water. The vessel was kept at 220 °C for 8 h. After cooling to room temperature, the hydrolyzed material was transferred to 500 ml of water and adjusted to *pH* 7 with ammonium hydroxide. The precipitate was removed by filtration, washed with water and air dried. The yield of crude product was 2.5 g (82%), m.p. 136–138 °C. The steam distilled product including that obtained by evaporating the mother liquor after removal of **IVa** was 2.2 g (72%), m.p. 142–144 °C. (Ref. [11] m.p. 144 °C, yield 46%. The yield of **IVa** starting from 4-chloro-2-nitroaniline was 69%).

6-Bromo-8-quinolinol (**IVb**)

The title compound was prepared from **IIIb** in the same manner as **IVa** was prepared from **IIIa**. The yield of product from a 0.015 *M* run was 2.5 g (74%), m.p. 144–145 °C. (Ref. [11] m.p. 143–145 °C, yield 33% from 2-acetamido-5-bromophenylacetate. The yield from 4-bromo-2-nitroaniline was 40%).

3,6-Dichloro-8-quinolinol (**VIIIa**)

Compound **VIIIa** was prepared from **VIIa** in the same manner as **IVa** was prepared from **IIIa** except that the hydrolysis liquid was composed of 8.4 ml of water and 19.5 g of sulfuric acid. The yield of product from a 0.014 *M* run was 3 g (94%), m.p. 145–147 °C. Upon steam distillation the melting point rose to 153–154 °C. An analytical sample was prepared by crystallization from 95% ethanol, m.p. 156–157 °C. Anal.: calcd. for $C_9H_5Cl_2NO$: C 50.50, H 2.35, Cl 33.05, N 6.55; found: C 50.29, H. 2.49, Cl 33.12, N 6.41.

3,6-Dibromo-8-quinolinol (**VIIIb**)

The title compound was prepared from **VIIb** in the same manner as **VIIIa** was prepared from **VIIa**. The yield of product from a 0.015 mol run was 4 g (89%), m.p. 165 °C. After steam distillation the m.p. rose to 171–175 °C. The analytical sample was crystallized from 95% ethanol, m.p. 181–182 °C. Anal.: calcd. for $C_9H_5Br_2NO$: C 35.68, H 1.66, Br 52.75, N 4.62; found: C 35.81, H 1.89, Br 53.10, N 4.35.

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