Monatshefte für Chemie 133, 1325–1330 (2002)
DOI 10.1007/s00706-002-0495-6

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Preparation and Antifungal Activity of 3-Iodo- and 6-Iodo-8-quinolinols

Herman Gershon[1,2,*], **Donald D. Clarke**[1], **John J. McMahon**[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

Received May 15, 2002; accepted June 11, 2002
Published online September 2, 2002

Summary. 3-Iodo- and 6-Iodo-8-quinolinols were prepared and tested against six fungi: *Aspergillus niger*, *A. oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes* in *Sabouraud* dextrose broth. A comparison with the previously known 5-iodo- and 7-iodo-8-quinolinols showed that the 6-iodo isomer was the most active.

Keywords. 3-Iodo-8-quinolinol; 6-Iodo-8-quinolinol; Antifungal activity.

Introduction

A monoiodo-8-quinolinol (m.p. 127–128°C) had been reported in 1927 [1]. Although the structure had not been established, it had been accepted as ''5-iodo-8-quinolinol''. Because of our interest in the antifungal activities of halo-8-quinolinols, we prepared what we believed to be ''7-iodo-8-quinolinol'' (m.p. 112–113°C) [2]. This structure was assigned because the two monoiodo-8-quinolinols had different melting points and a mixture of the two resulted in a depressed melting point.

In 1995 a monoiodo-8-quinolinol (m.p. 135°C) had been prepared by a procedure similar to that for ''5-iodo-8-quinolinol'' and had been reported to be 7-iodo-8-quinolinol [3]. The assignment of structure had been based on the ^{1}H decoupled ^{13}C NMR spectrum, which we found to be similar to that of the spectrum of ''5-iodo-8-quinolinol''. To establish unequivocally which of these compounds was 5- or 7-iodo-8-quinolinol, a crystal of monoiodo-8-quinolinol (m.p. 127–128°C) suitable for X-ray crystal structure determination had been prepared. It was found that this compound was in fact, 7-iodo-8-quinolinol [4]. Consequently, the monoiodo-8-quinolinol, m.p. 112–113°C was really 5-iodo-8-quinolinol.

Because of our interest in the antifungal properties of the halo-8-quinolinols, we undertook the preparation of 3-iodo- and 6-iodo-8-quinolinols.

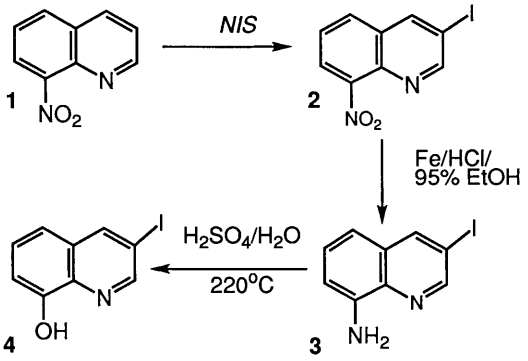
* Corresponding author. E-mail: clarke@fordham.edu

Results and Discussion

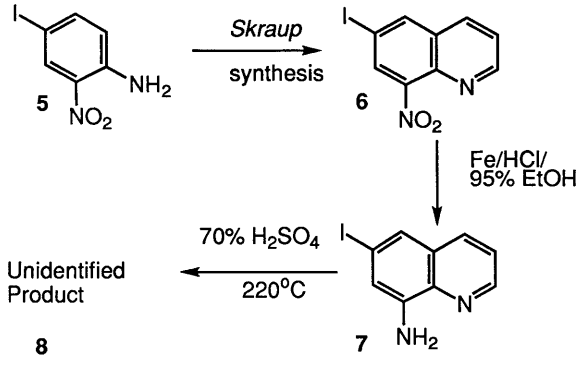
For the preparation of 3-iodo-8-quinolinol, the methods employed in the synthesis of the 3-chloro and 3-bromo analogues [5] were used. 8-Nitroquinoline (**1**) was iodinated at position 3 with *N*-iodosuccinimide (*NIS*), the nitro group reduced, and the amino group hydrolysed to yield 3-iodo-8-quinolinol (**4**) (Scheme 1) in an overall yield of 55% starting from **1**.

6-Chloro and 6-bromo-8-quinolinols have been prepared in high yield from their respective 8-aminoquinolines by hydrolysis with 70% sulfuric acid at 220°C [5]. However the same route was unsuccessful for the preparation of 6-fluoro-8-quinolinol. The product of that hydrolysis was not volatile on steam distillation and has not been characterized [6]. Since in aromatic bimolecular substitution the order of halogen as a leaving group is F>I>Br>Cl, it was thought that some 6-iodo-8-quinolinol (**11**) might survive the sulfuric acid hydrolysis conditions of 8-amino-6-iodoquinoline (**7**). 4-Iodo-2-nitroaniline (**5**) was prepared from 2-nitroaniline by iodination with *NIS*. A *Skraup* synthesis starting with **5** yielded 6-iodo-8-nitroquinoline (**6**), which was reduced to the 8-amino analogue **7** and hydrolyzed with 70% sulfuric acid at 220°C. No volatile product was obtained on steam distillation (Scheme 2).

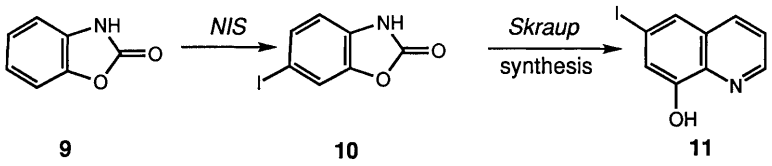
A *Skraup* synthesis starting with 2-amino-5-fluorophenol [7] has yielded the desired 6-fluoro-8-quinolinol [7]. We thus decided to use a similar approach for



Scheme 1



Scheme 2



9 10 11

Scheme 3

Table 1. Comparison of the antifungal activity of 3-iodo-, 5-iodo-, 6-iodo-, and 7-iodo-8-quinolinols in *Sabouraud* dextrose broth at 28°C in shake culture after six days

8-Quinolinol	Minimal inhibitory concentrations/[mmol · dm^{-3} (μgcm^{-3})]		
	A. niger	*A. oryzae*	*M. verrucaria*
3-iodo (**4**)	0.033 (9)	0.015 (4)	0.0074 (2)
5-iodo[a]	0.018 (5)	0.026 (7)	0.0074 (2)
6-iodo (**11**)	<0.0037 (<1)[b]	0.0074 (2)	<0.0037 (<1)[b]
7-iodo[a]	0.0074 (2)	0.011 (3)	<0.0037 (<1)[b]
8-Quinolinol	*T. viride*	*M. cirinelloides*	*T. mentagrophytes*
3-iodo (**4**)	0.030 (8)	0.15 (40)	0.018 (5)
5-iodo[a]	0.030 (8)	0.15 (40)	0.0074 (2)
6-iodo (**11**)	0.0074 (2)	0.037 (10)	<0.0037 (<1)[b]
7-iodo[a]	0.015 (4)	0.037 (10)	<0.0037 (<1)[b]

[a] Taken from Refs. [8, 9]; [b] < indicates below 1 μg/cm^3 (the lowest level tested); MICs from 1–10 were obtained in increments of 1 and from 11–20 in increments of 2 μg/cm^3

the preparation of 6-iodo-8-quinolinol (**11**). Iodination of benzoxazolinone-2 (**9**) with *NIS* yielded 6-iodo-benzoxazolinone-2 (**10**) which was hydrolyzed to 2-amino-5-iodophenol *in situ* under the conditions of the *Skraup* synthesis, and was then converted to **11** (Scheme 3). The over-all yield from **9** was 2.7%, and the amount obtained was 0.3 g, which was sufficient for characterization, antifungal evaluation, and preparation of the copper(II) biscomplex, which will be part of the subject for further study.

Table 1 contains the antifungal data of the four monoiodo-8-quinolinols against the six fungi in our test system: *Aspergillus niger*, *A. oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes*. Compound **11**, with the iodine in the 6 position, was the most fungitoxic of the four iodo analogues. This is consistent with the results for the 6-fluoro- [6] and for 6-chloro- and 6-bromo-8-quinolinols [10].

Experimental

Antifungal testing

Antifungal testing was performed in *Sabouraud* dextrose broth (Difco) according to published methods [8, 11–13]. The six fungi employed included *Aspergillus niger* (ATCC 1004), *A. oryzae* (ATCC 1011), *Myrothecium verrucaria* (ATCC 9095), *Trichoderma viride* (ATCC 8678), *Mucor cirinelloides* (ATCC 7941), *Trichophyton mentagrophytes* (ATCC 9129).

General

Melting points were taken on a *Thomas-Hoover* apparatus and are uncorrected. 8-Nitroquinoline and benzoxazolinone-2 were purchased from Aldrich. Reactions were monitored by gas chromatography using a Varian Aerograph Model 1400 gas chromatograph with a flame ionization detector to which a Varian Model 20 recorder was attached. The column employed was 5 feet × 1/8 inch o.d., packed with 10% SE-30 on Chromosorb W. Purity of products was established by ^{1}H and ^{13}C NMR spectroscopy at 300 MHz and 75 MHz with a Bruker DPX-300 spectrometer using *DMSO-d*$_6$ as solvent and *TMS* as internal standard. Elemental analyses matched the calculated values satisfactorily for **2**–**4** (C, H, I, N).

3-Iodo-8-nitroquinoline (**2**; $C_9H_5IN_2O_2$)

Compound **1** (34.8 g, 0.2 mol) was dissolved in 450 cm^3 acetic acid and 34.6 g *NIS* (0.2 mol) was added in portions over 1 h at near boiling. Heating under reflux was continued for 5 min, and let stir for 2 h at ambient temperatures. The solution was poured into 5000 cm^3 H_2O with stirring, and adjusted to *pH* 6 with NH_4OH. Product **2** was removed by filtration, washed with deionized H_2O, and air dried. Yield: 50.8 g (93%); m.p. 119–120°C (aq alc); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 9.15 (d, $J_{24} = 1.91$ Hz, H-2), 8.96 (d, H-4), 8.31 (d, $J_{57} = 2.74$ Hz, H-7), 8.17 (d, H-5), 7.81 (t, $J_{56} = 8.29$ Hz, $J_{67} = 7.42$ Hz, H-6) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 157.40 (C-2), 147.39 (C-8), 143.96 (C-4), 136.39 (C-8a), 131.33 (C-5), 129.64 (C-4a), 126.78 (C-6), 124.00 (C-7), 92.96 (C-3) ppm.

8-Amino-3-iodoquinoline (**3**; $C_9H_7IN_2$)

To a solution of 15 g (0.05 mol) of **2** in 670 cm^3 ethanol was added 10.5 g Fe powder (0.19 g atom) and 1 cm^3 HCl. The mixture was stirred vigorously under reflux for 3 h. The solids were removed by filtration, and the filtrate was poured into 5000 cm^3 H_2O with stirring. After 15 min, the precipitate was recovered by filtration, washed with H_2O and air dried. Yield: 12.5 g (93%); m.p. 129°C (aq alc); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.87 (d, $J_{24} = 2.02$ Hz, H-2), 8.64 (d, H-4), 7.37 (t, $J_{56} = 7.85$ Hz, $J_{67} = 7.86$ Hz, H-6), 7.03 (d, H-5), 6.99 (d, H-7), 3.93 (s, NH_2) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 151.56 (C-2), 145.15 (C-8), 143.26 (C-4), 135.25 (C-8a), 130.29 (C-4a), 128.69 (C-6), 112.93 (C-5), 109.61 (C-7), 90.83 (C-3) ppm.

3-Iodo-8-quinolinol (**4**; C_9H_6INO)

A mixture of 8.1 g (0.03 mol) of **3**, 14.3 cm^3 H_2O, and 9.5 cm^3 H_2SO_4 in a glass tube was sealed in a stainless steel pressure vessel containing a small amount of H_2O. The pressure vessel was heated at 220°C for 8 h. After cooling to room temperature, the contents of the glass tube were poured into 800 cm^3 deionized H_2O, brought to *pH* 6–7 with NH_4OH, and steam distilled. The solid product **4** was obtained by filtration and air dried. The distillate was reduced to half its volume under a stream of air and steam distilled a second time. An additional yield of **4** was obtained and air dried. Yield: 5.2 g (64%); m.p. 139–141°C (CH_3CN); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.99 (d, $J_{24} = 1.97$ Hz, H-2), 8.82 (d, H-4), 7.51 (dd, $J_{56} = 7.90$ Hz, H-6), 7.37 (d, H-5), 7.17 (d, $J_{67} = 7.45$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 153.78 (C-8), 153.18 (C-2), 143.94 (C-4), 136.89 (C-8a), 130.90 (C-4a), 128.98 (C-6), 117.33 (C-5), 112.75 (C-7), 91.64 (C-3) ppm.

4-Iodo-2-nitroaniline (**5**; $C_6H_5IN_2O_2$)

A mixture of 330 cm^3 acetic acid, 27.6 g (0.2 mol) 2-nitroaniline, and 47 g (0.21 mol) *NIS* was heated to 95°C over 1 h until the starch-iodide test was negative. The reaction mixture was poured into 3000 cm^3 H_2O, stirred 15 min, and the solids removed by filtration, washed with H_2O and air dried. Yield: 52.6 g (quant); m.p. 123–124°C (95% alc) (Ref. [14] m.p. 122°C, yield not given); ^{1}H NMR (300 MHz, δ,

DMSO-d_6): 8.22 (d, $J_{35} = 1.96$ Hz, H-3), 7.61 (dd, H-5), 7.59 (s, NH_2), 6.89 (d, $J_{56} = 8.96$ Hz, H-6) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 145.54 (C-1), 143.06 (C-5), 132.87 (C-3), 131.30 (C-2), 121.46 (C-6), 74.75 (C-4) ppm.

6-Iodo-8-nitroquinoline (**6**; $C_9H_5IN_2O_2$)

A mixture was prepared of 10 g H_2SO_4 (0.1 mol), 10 g glycerol (0.11 mol), and 5 g As_2O_5 (0.022 mol) and warmed with stirring until a solution was formed. 5 g of compound **5** (0.02 mol) was added in portions with stirring and continued heating. The mixture was refluxed for 3 h, cooled and poured into 450 cm^3 H_2O with stirring. The solids were removed by filtration, and the filtrate adjusted to *pH* 7 with NH_4OH. The precipitate was filtered off, washed with H_2O and air dried. Yield: 12 g (50%); m.p. 175–177°C (95% alc) (Ref. [15] m.p. 180°C (alc), yield 53%); ^{1}H NMR (300 MHz, δ, *DMSO-d_6*): 9.06 (q, $J_{23} = 4.20$ Hz, $J_{24} = 1.47$ Hz, H-2), 8.75 (d, H-7), 8.50 (d, $J_{57} = 1.70$ Hz, H-5), 8.45 (q, H-4), 7.78 (d, $J_{34} = 7.00$ Hz, H-3) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 153.05 (C-2), 147.83 (C-8), 140.18 (C-5), 137.26 (C-8a), 135.47 (C-4), 130.66 (C-7), 130.04 (C-4a), 123.91 (C-3), 89.87 (C-6) ppm.

8-Amino-6-iodoquinoline (**7**; $C_9H_7IN_2$)

A mixture of 3 g **6** (0.01 mol), 2.1 g Fe powder (0.038 mol), 135 cm^3 95% alc, and 0.2 cm^3 HCl was heated under reflux for 3 h with vigorous stirring. The suspension was filtered while hot, and the filtrate poured into 1000 cm^3 H_2O with stirring for 15 min. Product **7** was removed by filtration, washed with H_2O, air dried, and steam distilled. Yield: 2.3 g (85%); m.p. 108°C (alc) (Ref. [15] m.p. 108°C (alc), yield 58%); ^{1}H NMR (300 MHz, δ, *DMSO-d_6*): 8.74 (q, $J_{24} = 1.65$ Hz, H-2), 8.12 (q, $J_{34} = 8.31$ Hz, H-4), 7.47 (d, $J_{57} = 2.74$ Hz, H-5), 7.17 (q, H-3) 6.20 (d, H-7) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 147.31 (C-2), 146.62 (C-8), 136.35 (C-8a), 134.62 (C-4), 130.02 (C-4a), 122.21 (C-5), 121.48 (C-3), 116.14 (C-7), 94.25 (C-6) ppm. ^{1}H NMR (300 MHz, δ, *$CDCl_3$*): 8.72 (q, $J_{23} = 4.16$, $J_{24} = 1.52$ Hz, H-2), 7.90 (q, $J_{34} = 8.31$ Hz, H-4), 7.49 (d, $J_{57} = 1.51$ Hz, H-5), 7.34 (q, H-3), 7.15 (d, H-7), 5.06 (s, NH_2) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 147.58 (C-2), 144.89 (C-8), 1337.26 (C-8a), 134.76 (C-4), 130.12 (C-4a), 124.41 (C-5), 1222.07 (C-3), 118.13 (C-7), 93.36 (C-6) ppm.

Unidentified (**8**)

Compound **7** (5.4 g, 0.02 mol) and 50 cm^3 70% H_2SO_4 (*w*/*w*) in a glass container were sealed in a stainless steel pressure vessel containing a small amount of H_2O. The vessel was kept at 220°C for 8 h and cooled. The mixture was diluted with 500 cm^3 H_2O, adjusted to *pH* 6–7 with NH_4OH, and steam distilled. No volatile product was obtained, and the residue was not characterized.

6-Iodobenzoxazolinone-2 (**10**; $C_7H_4INO_2$)

A mixture of 1.4 g (0.01 mol) benzoxazolinone-2, (**9**), 2.3 g *NIS* (0.01 mol), and 200 cm^3 acetic acid was stirred at ambient temperatures for 5 days and monitored by g.c. Additional *NIS* was added if needed until all of **9** was iodinated. The solution was transferred to 1200 cm^3 H_2O, stirred for 15 min, and **10** was removed by filtration, washed with H_2O and air dried. Yield: 2.4 g (96%); m.p. 217–218°C (95% alc) (Ref. [16] m.p. 211–212°C, yield 12%); ^{1}H NMR (300 MHz, δ, *DMSO-d_6*): 8.88 (dd, $J_{23} = 4.18$ Hz, $J_{24} = 1.01$ Hz, H-2), 8.29 (dd, $J_{34} = 8.37$ Hz, H-4), 7.88 (d, $J_{57} = 1.39$ Hz, H-5), 7.59 (dd, H-3), 7.38 (d, H-7) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 154.06 (C-2), 143.99 (C-1a), 132.36 (C-5), 130.15 (C-3a), 117.81 (C-7), 111.88 (C-4), 83.62 (C-6) ppm.

6-Iodo-8-quinolinol (**11**; C_9H_6INO)

A mixture of 20 g H_2SO_4 (0.2 mol), 20.2 g glycerol (0.22 mol), 10.1 g As_2O_5 (0.044 mol), and 10.4 g **10** (0.04 mol) was prepared in that order with stirring. It was heated slowly until boiling, and kept under

reflux for 2 h. After cooling below 100°C the liquid was poured into 250 cm^3 deionized H_2O, adjusted to *pH* 6–7 with NH_4OH, and steam distilled. The product **11** was obtained by filtration and air dried. Yield: 0.3 g (2.8%); m.p. 139–141°C (CH_3CN); HR-MS: calcd. for C_9H_6INO: 270.94942, found: 270.94856; ^1H NMR (300 MHz, δ, *DMSO-d_6*): 8.88 (dd, $J_{23} = 4.18$ Hz, $J_{24} = 1.01$ Hz, H-2), 8.29 (dd, $J_{34} = 8.37$ Hz, H-4), 7.88 (d, $J_{57} = 1.39$ Hz, H-5), 7.59 (dd, H-3), 7.38 (d, H-7) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d_6*): 153.86 (C-8), 148.59 (C-2), 137.40 (C-8a), 135.21 (C-4), 130.28 (C-4a), 126.28 (C-5), 122.63 (C-3), 119.84 (C-7), 93.03 (C-6) ppm.

Acknowledgments

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

References

[1] Matsumura (1927) J Am Chem Soc **49**: 810
[2] Gershon H, McNeil MW (1971) J Heterocycl Chem **8**: 129
[3] Ramelo CT, Faez R, Ribeiro CA, Crespi MS (1995) Ecl Quim Sao Paulo **20**: 49
[4] Shoja M, Gershon H, Clarke DD (1997) Zeit Kristall NCS **212**: 387
[5] Gershon H, Clarke DD (1991) Monatsh Chem **122**: 935
[6] Gershon H, Clarke DD, Gershon M (2002) Monatsh Chem, in press
[7] Levy LA, Murphy E, Raju B, London RE (1988) Biochemistry **27**: 4041
[8] Gershon H, Clarke DD, Gershon M (1989) J Pharm Sci **78**: 975
[9] Gershon H, Clarke DD, Gershon M (1991) J Pharm Sci **80**: 542
[10] Gershon H, Clarke DD, Gershon M (1994) Monatsh Chem **125**: 51
[11] Gershon H, Shanks L (1981) Can J Microbiol **27**: 612
[12] Gershon H, Grefig AT, Cady DJ (1985) Can J Microbiol **31**: 707
[13] Gershon H, Clarke DD, Gershon M (1993) Monatsh Chem **124**: 367
[14] Brennan P (1914) Compt Rend **158**: 717
[15] Hamada Y, Sugihara H, Ito K, Tomamatsu S (1966) Yakugaki Zasshi **86**: 224
[16] Eckstein Z, Zukowski E (1958) Przmsl Chem **37**: 418