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Preparation of 6-Fluoro-8-quinolinol and Related 6-Fluoroquinolines

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Summary. 6-Fluoro-8-quinolinol was prepared from 2-amino-5-fluorophenol by a *Skraup* synthesis. No synergism was observed between 5-fluoro- and 6-fluoro-8-quinolinols or between 6-fluoro- and 7-fluoro-8-quinolinols against any of the six fungi in our test system (*Aspergillus niger*, *A. oryzae*, *Myrothecium verrucaria*, *Trichoderma viride*, *Mucor cirinelloides*, and *Trichophyton mentagrophytes*) in *Sabouraud* dextrose broth. Unlike the fluoro-8-quinolinols, the 8-quinolinols comparably substituted with chlorine or bromine did form synergistic mixtures. This is attributed to steric factors.

Keywords. 6-Fluoro-8-quinolinol; Antifungal activity.

Introduction

5-Fluoro- [1] and 7-fluoro-8-quinolinols [2] had been prepared previously. These are the only monofluoro-8-quinolinols reported to this time. All the possible monochloro and monobromo compounds [3] have been prepared and tested against the six fungi [4] in our test system. It was considered of interest to pepare additional monofluoro-8-quinolinols.

Results and Discussion

Since the 5-fluoro- and 7-fluoro-8-quinolinols were obtained in satisfactory yields from the corresponding amino-8-quinolinols by the *Baltz-Schiemann* reaction, we attempted to prepare 6-fluoro-8-quinolinol from 6-amino-8-quinolinol in the same manner. The product obtained was a mixture of approximately 50% 6-fluoro-8-quinolinol and 25% each of the 5-fluoro- and 7-fluoro- analogues as determined by ^{19}F NMR spectroscopy. The mixture proved to be difficult to separate, and therefore this approach was abandoned.

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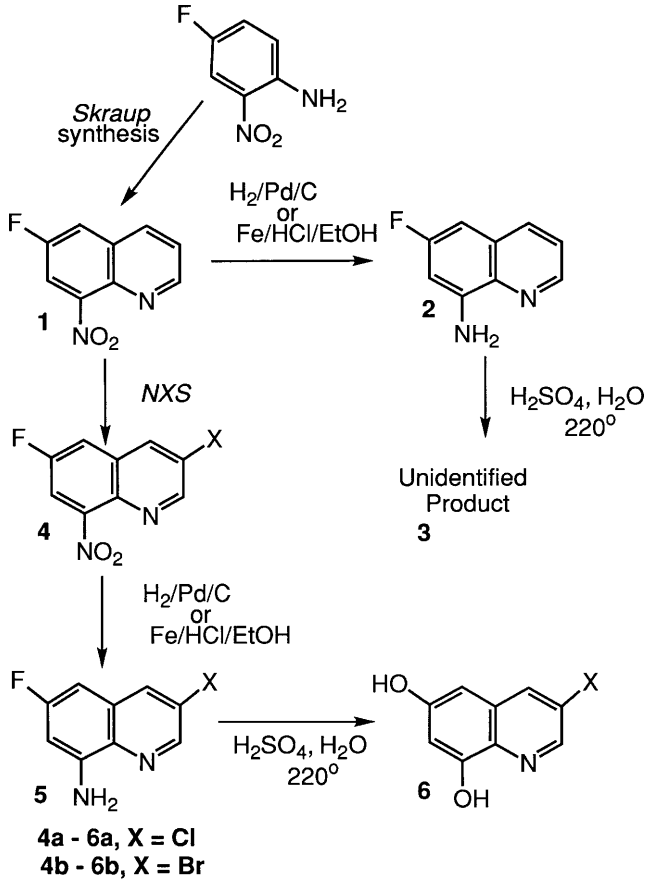
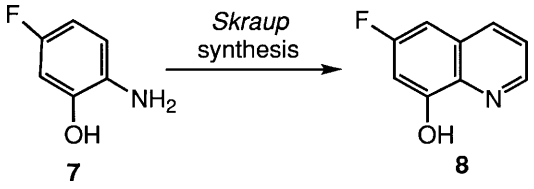


Scheme 1

In our earlier work on the peparation of 3,6-dichloro- and 3,6-dibromo-8-quinolinols [5] as well as 3-bromo-6-chloro- and 6-bromo-3-chloro-8-quinolinols [6], we have found that the 6-bromo- and 6-chloro substituents were resistant to hydrolysis in 70% sulfuric acid at 200°C. It was decided to undertake the approach in which 8-amino-6-fluoroquinoline, as well as its 3-bromo and 3-chloro analogues were hydrolyzed in 70% sulfuric acid. The purification of the products was by steam distillation. This synthetic sequence is outlined in Scheme 1. The known compound 6-fluoro-8-nitroquinoline (**1**) [7], was reduced to 8-amino-6-fluoroquinoline (**2**) [7] and subjected to hydrolysis by 70% aqueous sulfuric acid at 200°C for 8 h. The product **3** was not volatile with steam as expected and was not isolated.

Since halogen in position 3 of 8-quinolinol seemed to stabilize the halogen in position 6 toward hydrolysis by sulfuric acid [4, 5], we halogenated **1** with the respective *N*-halosuccinimide (*NXS*) to yield 3-chloro-6-fluoro-8-nitroquinoline (**4a**) and 3-bromo-6-fluoro-8-nitroquinoline (**4b**). These were reduced to the amines **5a**, and **5b** followed by sulfuric acid hydrolysis. 3-Chloro-6-8-dihydroxyquinoline (**6a**) was obtained in 90% yield and the bromo analogue, **6b** was produced in 97% yield. None of the expected products containing fluorine were obtained.



Scheme 2

A successful preparation of 6-fluoro-8-quinolinol (**8**) in 57% yield was achieved by a *Skraup* synthesis starting with 2-amino-5-fluorophenol (**7**) [8] (Scheme 2).

The fluorination of 8-quinolinol in position 3 was attempted. Based on the ease of halogenation of 8-nitroquinoline in the 3 position and the stability of halogen in this position to the conditions of hydrolysis of the amino group at 200°C in the presence of 70% sulfuric acid [4, 5], we attempted fluorinating 8-nitroquinoline and its 6-bromo and 6-chloro analogues with electrophilic fluorinating agents (*N*-fluorobenzenesulfonimide [9] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octanebis(tetrafluoroborate) [10]. No fluorination was observed, and 3-fluoro-8-quinolinol has yet to be made.

5-Chloro- and 7-chloro-, 5-bromo- and 7-bromo-, and 5-iodo- and 7-iodo-8-quinolinols have formed synergistic mixtures, whereas 5-fluoro- and 7-fluoro- 8-quinolinols did not [11]. This has been rationalized on the basis of steric effects introduced into the molecule by the halogen substituent. Since fluorine and hydrogen are nearly isosteric, it would not be expected to observe synergism between mixtures of 5-fluoro- and 7-fluoro-8-quinolinols [11]. When minimal inhibitory concentrations (MICs) of 5-fluoro- and 6-fluoro-8-quinolinols or 6-fluoro- and 7-fluoro-8-quinolinol were tested against the fungi only additivity of toxicity was observed. This is consistent with results reported earlier. Table 1 contains data comparing the fungitoxicity of the three monofluoro-8-quinolinols.

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

Minimal Inhibitory Concentrations/mmol dm^{-3} ($\mu g\,cm^{-3}$)[a]			
8-Quinolinol	*A. niger*	*A. oryzae*	*M. verrucaria*
5-fluoro[b]	0.11 (18)	0.086 (14)	0.025 (4)
6-fluoro (8)	0.025 (4)	0.025 (4)	< 0.0062 (< 1)
7-fluoro[b]	0.049 (8)	0.025 (4)	0.018 (3)
8-Quinolinol	*T. viride*	*M. cirinelloides*	*T. mentagrophytes*
5-fluoro[b]	0.11 (18)	0.016 (26)	0.025 (4)
6-fluoro (8)	0.025 (4)	0.025 (4)	0.012 (2)
7-fluoro[b]	0.037 (6)	0.037 (6)	0.012 (2)

[a] MICs from 1–10 were obtained in increments of 1 and from 11–20 in increments of 2 $\mu g/cm^3$, < indicates below 1 $\mu g/cm^3$ (the lowest level tested); [b] Taken from Ref. [11]

Experimental

Antifungal Testing

Antifungal testing was performed in *Sabouraud* dextrose broth (Difco) according to Refs. [12–15]. The fungi employed included *Aspergillus niger* (ATCC 1004), *A. 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. 5-Fluoro-2-nitrophenol and 4-fluoro-2-nitroaniline 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 $\times$ 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 **4a**, **5a** (C, H, Cl, F, N), **4b**, **5b** (C, H, Br, F, N),and **8** (C, H, F, N).

6-Fluoro-8-nitroquinoline (**1**)

A mixture was prepared to which 117.8 g of H_2SO_4, 50.4 cm^3 of H_2O, 58.4 g (0.213 mol) of sodium 3-nitrobenzene sulfonate, and 52.8 cm^3 of glycerol were added in that order. It was warmed gently with stirring to form a solution, and 31.2 g 4-fluoro-2-nitroaniline (0.20 mol) was added in portions. The mixture was heated to reflux slowly with vigorous stirring and continued for 4 h. After cooling, the mixture was diluted with 2000 cm^3 H_2O and adjusted to *pH* 6–7 with NH_4OH. The product was recovered by filtration, washed with H_2O, and dried at 50°C. Yield 26 g (68%); mp 122–123°C (aq alc) (Ref. [7]: mp 119.2–120°C (benzene), yield (46%); ^{1}H NMR (300 MHz, δ, *DMSO-*d_6): 9.07 (dd, $J_{23} = 4.2$ Hz, $J_{24} = 1.6$ Hz, H-2), 8.57 (dd, $J_{34} = 8.3$ Hz, H-4), 8.50 (dd, $J_{57} = 2.8$ Hz, $J_{6F7H} = 8.0$ Hz, H-7), 8.17 (dd, $J_{5H6F} = 9.0$ Hz, H-5), 7.80 (dd, $J_{34} = 8.3$ Hz, H-3) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-*d_6): 157.5 ($J_{CF} = 248.3$ Hz, C-6), 152.2 ($J_{CF} = 2.3$ Hz, C-2), 148.6 ($J_{CF} = 10.3$ Hz, C-8), 136.1 ($J_{CF} = 5.2$ Hz, C-4), 135.7 ($J_{CF} = 1.4$ Hz, C-8a), 129.2 ($J_{CF} = 10.4$ Hz, C-4a), 124.0 ($J_{CF} = < 1$ Hz, C-3), 115.2 ($J_{CF} = 21.7$ Hz, C-5), 114.1 ($J_{CF} = 31.5$ Hz, C-7) ppm.

8-Amino-6-fluoroquinoline (**2**)

A mixture containing 19.2g **1** (0.1 mol) and 3 g 10% Pd/C in 250 cm^3 CH_3OH was subjected to 3 atm of H_2 in a *Parr* hydrogenator. After the theoretical quantity of H_2 was taken up, the mixture was freed of catalyst by filtration, and the solvent was evaporated under a stream of air. Yield 15.6 g (96%): mp 49–50°C (aq alc) (Ref. [7]: mp 50–50.6°C (aq alc), yield (79%); ^{1}H NMR (300 MHz, δ, *DMSO-*d_6): 8.75 (dd, $J_{23} = 4.1$ Hz, $J_{24} = < 1.0$ Hz, H-2), 8.20 (dd, $J_{34} = 8.3$ Hz, H-4), 7.54 (dd, H-3), 6.87 (dd, J_{7H6F} 9.6 Hz, H-7), 6.83 (dd, $J_{57} = 2.8$ Hz, $J_{6F5H} = 11.3$ Hz, H-5) 6.40 (s, NH_2) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-*d_6): 161.4 ($J_{CF} = 241.2$ Hz, C-6), 147.7 ($J_{CF} = 13.9$ Hz, C-8), 146.4 ($J_{CF} = 2.3$ Hz, C-2), 135.7 ($J_{CF} = 5.74$ Hz, C-4), 135.0 ($J_{CF} = < 1$ Hz, C-8a), 129.3 ($J_{CF} = 13.1$ Hz, C-4a), 122.6 ($J_{CF} = < 1$ Hz, C-3), 97.6 ($J_{CF} = 29.1$ Hz, C-7), 96.6 ($J_{CF} = 22.4$ Hz, C-5) ppm.

3-Chloro-6-fluoro-8-nitroquinoline (**4a**, $C_9H_4ClFN_2O_2$)

To 200 cm^3 of acetic acid were added 12.5 g **1** (0.065 mol) and 8.7 g *NCS* (0.065 mol). The mixture was heated to 50°C with stirring for 5 h. Unreacted **1** was still present as shown by gas chromatography.

Additional *NCS* was added equal to unreacted **1**. Heating and stirring were continued for 1 h and then brought to boiling. This may have to be repeated until the gas chromatogram indicates the absence of **1**. The solution was poured into 1200 cm^3 H_2O with stirring, and the product was removed by filtration and air dried. Yield 12 g (82%); mp 158°C (aq alc, Darco G-60); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.97 (d, $J_{24} = 2.3$ Hz, H-2), 8.86 (d, H-4), 8.40 (dd, $J_{57} = 2.8$ Hz, $J_{6F7H} = 8.8$ Hz, H-7), 8.07 (dd, $J_{5H6F} = 7.9$ Hz, H-5), ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 158.3 ($J_{CF} = 250.5$ Hz, C-6), 150.9 ($J_{CF} = 2.7$ Hz, C-2), 148.2 ($J_{CF} = 10.4$ Hz, C-8), 134.2 ($J_{CF} = 5.3$ Hz, C-4), 133.7 ($J_{CF} = 15.9$ Hz, C-8a), 130.5 ($J_{CF} = < 1$ Hz, C-3), 129.5 ($J_{CF} = 10.7$ Hz, C-4a), 114.9 ($J_{CF} = 14.9$ Hz, C-5), 114.6 ($J_{CF} = 24.1$ Hz, C-7) ppm.

3-Bromo-6-fluoro-8-nitroquinoline (**4b**, $C_9H_4BrFN_2O_2$)

Compound **4b** was prepared from **1** in the same manner as **4a** was from **1**. *NBS* was the halogenating agent in place of *NCS*, and the reaction was based on a 0.1 mol run. Yield: 26 g (96%); mp 165–166°C (95% alc, Darco G-60); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 9.08 (d, $J_{24} = 1.8$ Hz, H-2), 8.87 (d, H-4), 8.53 (dd, $J_{57} = 2.6$ Hz, $J_{7H6F} = 8.0$ Hz, H-7), 8.10 (dd, $J_{5H6F} = 8.8$ Hz, H-5), ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 158.1 ($J_{CF} = 250.1$ Hz, C-6), 152.7 ($J_{CF} = 2.6$ Hz, C-2), 148.4 ($J_{CF} = 10.5$ Hz, C-8), 137.4 ($J_{CF} = 5.4$ Hz, C-4), 133.9 ($J_{CF} = < 1$ Hz, C-8a), 130.0 ($J_{CF} = 10.8$ Hz, C-4a), 119.7 ($J_{CF} = < 1$ Hz, C-3), 114.72 ($J_{CF} = 32.0$ Hz, C-7), 114.65 ($J_{CF} = 22.1$ Hz, C-5) ppm.

8-Amino-3-chloro-6-fluoroquinoline (**5a**, $C_9H_6ClFN_2$)

To a solution of 9.1 g **4a** (0.04 mol) in 250 cm^3 ethanol was added 8.4 g Fe powder (0.14 mol) and 0.8 cm^3 HCl. The suspension was stirred under reflux for 3 h. The solids were filtered off, and the solvent evaporated under a stream of air to yield **5a**. Yield 7.9 g (100%); mp 127–128°C (sublimation); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.63 (d, $J_{24} = 2.3$ Hz, H-2), 8.32 (d, H-4), 6.78 (dd, $J_{7H6F} = 9.7$ Hz, H-7), 6.70 (dd, $J_{57} = 2.7$ Hz, $J_{6F5H} = 11.5$ Hz, H-5) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 162.1 ($J_{CF} = 242.6$ Hz, C-6), 148.0 ($J_{CF} = 14.4$ Hz, C-8), 144.6 ($J_{CF} = 2.6$ Hz, C-2), 133.5 ($J_{CF} = 5.8$ Hz, C-4), 132.9 ($J_{CF} = < 1$ Hz, C-8a), 129.8 ($J_{CF} = 13.8$ Hz, C-4a), 128.9 ($J_{CF} = < 1$ Hz, C-3), 97.5 ($J_{CF} = 29.1$ Hz, C-7), 95.7 ($J_{CF} = 23.7$ Hz, C-5) ppm.

8-Amino-3-bromo-6-fluoroquinoline (**5b**, $C_9H_6BrFN_2$)

Compound **5a** was reduced to **5b** in the same manner as **4a** was converted to **5a**. The reaction was carried out on 0.08 mol of **4b**. Yield 17 g (88%); mp 145°C (aq alc); ^{1}H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.71 (s, H-2), 8.49 (s, H-4) 6.68–6.78 (m, H-5 and H-7), 6.45 (s, NH_2) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 161.9 ($J_{CF} = 242.5$ Hz, C-6), 148.1 ($J_{CF} = 14.34$ Hz, C-8), 146.3 ($J_{CF} = < 1$ Hz, C-2), 136.7 ($J_{CF} = 5.5$ Hz, C-4), 133.0 ($J_{CF} = < 1$ Hz, C-8a), 130.5 ($J_{CF} = 13.9$ Hz, C-4a), 118.1 ($J_{CF} = < 1$ Hz, C-3), 97.5 ($J_{CF} = 29.0$ Hz, C-5), 95.6 ($J_{CF} = 23.6$ Hz, C-7) ppm.

3-Chloro-6,8-dihydroxyquinoline (**6a**)

Compound **5a** (3.9 g, 0.02 mol) was hydrolyzed in the presence of 70% aq H_2SO_4 (*w*/*w*) in the same way as **3** was formed from **2**. Upon steam distillation of the mixture, no solid material volatilized. The residual aqueous solution was cooled to room temperature, and **6a** crystals formed which were recovered by filtration. Yield 3.5 g (90%); mp 182–183°C (aq alc, Darco G-60) (Ref. [6]: mp 182–184°C); NMR data in Ref. [6].

3-Bromo-6,8-dihydroxyquinoline (**6b**)

The method of preparation of **6b** and **5b** was the same as for **6a** from **5a**. The results are based on a 0.015 mol run. Yield 3.5 g (97%); mp 179–180°C (aq alc, Darco G-60) (Ref. [6]: mp 179–180°C); NMR data in Ref. [6].

6-Fluoro-8-quinolinol (**8**, C_9H_6FNO)

A mixture of 47 g H_2SO_4, 20.2 cm^3 H_2O, 23.4 g sodium 3-nitrobenzensulfonate (0.1 mol), and 21.1 cm^3 glycerol was assembled in that order and heated until all went into solution. 2-Amino-5-fluorophenol [8] (10.2 g, 0.08 mol) was added to the warm solution with stirring and heating slowly until boiling. This was continued for 3.5 h under reflux. The mixture was cooled to about 80°C and poured into 1500 cm^3 deionized H_2O with stirring. It was brought to *pH* 6–7 with NH_4OH and steam distilled. The major yield of **8** was obtained by filtration. An additional yield of product was recovered by concentration of the filtrate under a stream of air. Yield 7.5 g (57%); mp 139–140°C (95% alc); ^1H NMR (300 MHz, δ, *DMSO-d*$_6$): 8.87 (dd, $J_{24} = 1.4$ Hz, $J_{23} = 4.1$ Hz, H-2), 8.35 (dd, $J_{34} = 8.4$ Hz, H-4), 7.63 (dd, H-3), 7.22 (dd, $J_{57} = 2.7$ Hz, $J_{5H6F} = 9.5$ Hz, H-5), 7.05 (dd, $J_{57} = 2.7$ Hz, $J_{7H6F} = 10.7$ Hz, H-7) ppm; ^{13}C NMR (75 MHz, δ, *DMSO-d*$_6$): 160.5 ($J_{CF} = 243.5$ Hz, C-6), 155.4 ($J_{CF} = 14.2$ Hz, C-8), 147.7 ($J_{CF} = 2.4$ Hz, C-2), 136.2 ($J_{CF} = 21.8$ Hz, C-8a), 135.9 ($J_{CF} = 5.9$ Hz, C-4), 129.0 ($J_{CF} = 12.8$ Hz, C-4a), 122.9 ($J_{CF} = < 1$ Hz, C-3), 101.6 ($J_{CF} = 28.6$ Hz, C-7), 100.9 ($J_{CF} = 22.2$ Hz, C-5) ppm.

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