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Improved Syntheses of Some Monochloro- and Monobromo-8-quinolinols

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Summary. Procedures were developed for the preparation of the 2-, 3-, 4-, and 6-monosubstituted chloro and bromo 8-quinolinols which afforded greater yields and/or reduced the number of steps in the preparation. 100 MHz ^{1}H-NMR spectra for the 12 possible monochloro and monobromo analogues are given.

Keywords. Monochloro-8-quinolinols; Monobromo-8-quinolinols; 2-Acetamido-5-halophenyl acetates; ^{1}H-NMR spectra.

Verbesserte Synthese von Monochlor- und Monobrom-8-chinolinolen

Zusammenfassung. Es wurden Verfahren entwickelt, um 2-, 3-, 4- und 6-Chlor bzw. -Brom-8-chinolinole in besseren Ausbeuten und/oder bei reduzierter Anzahl von Synthesestufen herzustellen. Die ^{1}H-NMR-Spektren der 12 möglichen Monochlor- und Monobromverbindungen werden angegeben.

Introduction

Due to our long standing interest in the antifungal properties of the substituted 8-quinolinols [1–8], it was necessary to obtain quantities of the six monochloro- and six monobromo-8-quinolinols for further study. Of these twelve compounds only the 5-chloro analogue is commercially available.

Results and Discussion

Chlorination of 8-acetoxy-2-quinolinol [9] with phosphorus oxychloride, followed by deacetylation, yielded 2-chloro-8-quinolinol. Its melting point agreed with that reported by Fleming and Pettit [10] who indicated that the product reported by Hamana and Funakoshi [11] melted too low. We observed the low melting form in a crude preparation which was converted to the higher melting product by recrystallization or by heating to 90–100°C. The ^{1}H-NMR spectrum of the low melting material showed a water peak at $\delta = 3.4$ ppm which integrated for 0.5 H_2O per molecule of compound. The 2-bromo analogue was prepared previously but not isolated [12]. The product reported herein was also prepared from 8-acetoxy-2-quinolinol by bromination with phosphorus oxybromide followed by hydrolysis.

3-Chloro-8-quinolinol [9] was prepared in 5% yield by a Doebner-Miller reaction. The present approach to the product was by chlorinating 8-nitroquinoline

Table 1. [1]H-NMR Spectra of the monochloro- and monobromo-8-quinolinols[a]

Compound	Chemical shifts (δ) ppm from *TMS*							Coupling constants (Hz)					
	Proton No.												
	2	3	4	5	6	7	O–H	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
O*X*[b]	8.91 (q)	7.57 (q)	8.36 (q)	7.48 (q)	7.46 (q)	7.22 (q)	9.90 (s)	4.0	1.5	8.5	8.0	1.1	7.8
2-Cl-O*X*	–	7.56 (d)	8.38 (d)	7.48 (q)	7.49 (q)	7.26 (q)	10.10 (s)	–	–	8.5	8.0	3.0	6.0
3-Cl-O*X*	8.80 (d)	–	8.50 (d)	7.41 (q)	7.53 (q)	7.19 (q)	10.10 (s)	–	2.3	–	8.0	1.5	7.0
4-Cl-O*X*	8.81 (d)	7.80 (d)	–	7.61 (q)	7.65 (q)	7.26 (q)	10.10 (s)	4.0	–	–	8.0	1.5	6.0
5-Cl-O*X*	9.00 (q)	7.75 (q)	8.51 (q)	–	7.64 (d)	7.18 (d)	10.20 (s)	4.0	1.5	8.5	–	–	8.5
6-Cl-O*X*	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	–
7-Cl-O*X*	8.92 (q)	7.60 (q)	8.36 (q)	7.46 (d)	7.56 (d)	–	9.50 (s)	4.0	1.5	8.5	9.0	–	–
2-Br-O*X*	–	7.74 (d)	8.35 (d)	7.54 (q)	7.56 (q)	7.31 (q)	10.17 (s)	–	–	8.5	8.0	2.5	7.0
3-Br-O*X*	8.95 (d)	–	8.67 (d)	7.44 (q)	7.54 (q)	7.25 (q)	10.20 (s)	–	2.0	–	8.0	1.5	7.0
4-Br-O*X*	8.76 (d)	8.00 (d)	–	7.61 (q)	7.65 (q)	7.29 (q)	10.20 (s)	4.5	–	–	8.0	2.0	6.0
5-Br-O*X*	9.03 (q)	7.79 (q)	8.49 (q)	–	7.84 (d)	7.16 (d)	10.30 (s)	4.0	1.5	8.5	–	–	8.0
6-Br-O*X*	8.96 (q)	7.63 (q)	8.35 (q)	7.71 (d)	–	7.30 (d)	10.20 (s)	4.0	1.5	8.5	–	2.0	–
7-Br-O*X*	9.00 (q)	7.69 (q)	8.45 (q)	7.45 (d)	7.75 (d)	–	10.30 (s)	4.0	1.5	8.5	9.0	–	–

[a] Spectra taken in *DMSO-d_6* with *TMS* as internal standard

[b] O*X* = 8-quinolinol

with sulfuryl chloride in *o*-dichlorobenzene in 84% yield or with N-chlorosuccinimide (*NCS*) in acetic acid in 96% yield. This compound was previously prepared in 43% yield by chlorination of 8-nitroquinoline with sulfur dichloride [13]. Hydrogenation of the nitro compound over 10% palladium on carbon afforded 93% of the amino derivative which was hydrolyzed at 220°C for 15 hours in 40% aqueous sulfuric acid. The yield of 3-chloro-8-quinolinol was 93%. The preparation of 3-bromo-8-quinolinol was carried out analogously using N-bromosuccinimide (*NBS*) as the brominating agent. 3-Bromo-8-nitro- and 3-bromo-8-aminoquinolines were both known compounds [14] as was 3-bromo-8-quinolinol [15]. By the previously published methods the overall yield of this compound was 26%, whereas by the present methods it was 79%.

Modifications of published methods were used to convert 4-hydroxy-8-methoxyquinoline [16] to 4-chloro-8-quinolinol [17, 18]. 4-Bromo-8-quinolinol was obtained from 4-hydroxy-8-methoxyquinoline in 80% overall yield by modification of the methods of Irving and Pinnington [15].

The preparation 6-chloro-8-quinolinol [19] and its bromo analogue [15] was by one-step Skraup reactions from the respective 2-acetamido-5-halophenyl acetates by the method of Hoffmann [19]. The yield of 6-bromo-8-quinolinol (33% yield) could not be compared with that published [15] since no yield of product was reported for the preparation of the intermediate 6-bromo-8-methoxyquinoline, which was subsequently hydrolyzed to 6-bromo-8-quinolinol.

The remaining monohalo-8-quinolinols were prepared by methods found in the literature: 5-bromo [20], 7-chloro [2] and 7-bromo [2]. The ^{1}H-NMR spectra of the monohalo-8-quinolinols are summarized in Table 1 and are consistent with the structures.

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Experimental

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The purity of samples was established by gas chromatography which 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 3% Dexsil 400 on Anachrom A (90–100 mesh) purchased from Analabs, New Haven, CT. Nitrogen was used as the carrier gas. ^{1}H-NMR spectra were obtained on a Varian XL-100 spectrometer using *DMSO-d_6* as solvent and *TMS* as internal standard.

8-Acetoxy-2-chloroquinoline

A suspension of 4.1 g (0.02 mol) of 8-acetoxy-2-quinolinol [9] in 41 ml of phosphorus oxychloride was heated with stirring under reflux for 25 h. The excess phosphorus oxychloride was removed on a rotary evaporator, and the residue was poured into a slurry of ice and water. The product was extracted with chloroform. The extract was washed with water, decolorized with carbon, dried over sodium sulfate and the solvent removed by distillation under reduced pressure. The yield of compound was 3.3 g (77%), m.p. 74–75°C. An analytical sample was crystallized from aqueous ethanol, m.p. 75–76°C.

Anal. calcd. for $C_{11}H_8ClNO_2$: C 59.61, H 3.64, Cl 16.00, N 6.36. Found: C 59.60, H 3.95, Cl 15.73, N 6.56. ^{1}H-NMR: $\delta = 7.96$ (d, 4-H), 7.54 (q, 6-H), 7.46 (q, 5-H), 7.42 (q, 7-H), 7.30 (d, 3-H), 2.46 [s, CH_3 (CH_3CO)], $J_{3,4} = 8$ Hz.

8-Acetoxy-2-bromoquinoline

To a solution of 8-acetoxy-2-quinolinol (11.6 g, 0.057 mol) in 35 ml of chloroform was added phosphorus oxybromide (40 g, 0.14 mol). The mixture was heated with stirring under reflux for 4 h, after which it was poured into a slurry of ice and water. After stirring for 10 min the mixture was filtered and the chloroform layer was separated. It was washed with water, decolorized with carbon and dried over sodium sulfate. Upon of evaporation of the chloroform, a residue of crude product remained (10 g, 66%), m.p. 63–65°C. An analytical sample was prepared by crystallization form aqueous ethanol, m.p. 71–72°C.

Anal. calcd. for $C_{11}H_8BrNO_2$: C 49.65, H 3.03, Br 30.03, N 5.27. Found: C 49.60, H 2.87, Br 29.74, N 5.16. ^{1}H-NMR: $\delta = 8.50$ (d, 4-H), 8.07 (q, 5-H), 7.86 (d, 3-H), 7.84 (q, 7-H), 7.78 (q, 6-H), 2.66 [s, CH_3 (CH_3CO)], $J_{3,4} = 8.5$ Hz, $J_{5,6} = 8$ Hz, $J_{5,7} = 2.3$ Hz, $J_{6,7} = 7$ Hz.

2-Chloro-8-quinolinol

A mixture of 8-acetoxy-2-chloroquinoline (5.6 g, 0.025 mol), potassium hydroxide (86%), (5.0 g, 0.075 mol) and 63 ml of ethanol was stirred for 1 h at ambient temperatures. Three volumes of water was added to form a clear solution which was brought to *pH* 6–7 with hydrochloric acid. The product that formed was recovered by steam distillation, filtration and drying. The yield of compound was 3.2 g (72%), m.p. 81.5–82.5°C (Lit. [10] m.p. 82–83°C, yield 67%).

2-Bromo-8-quinolinol

The title compound was prepared from 8-acetoxy-2-bromoquinoline in the same manner as for 2-chloro-8-quinolinol. The yield was 84%, m.p. 79.5–80.5°C. The analytical sample was crystallized from aqueous ethanol, m.p. 81–82°C.

Anal. calcd. for C_9H_6BrNO: C 48.24, H 2.07, Br 35.66, N 6.25. Found: C 48.08, H 2.29, Br 35.59, N 6.06.

3-Chloro-8-nitroquinoline

A. To a solution of 8-nitroquinoline (5.2 g, 0.03 mol) in 100 ml of *o*-dichlorobenzene was added sulfuryl chloride (6.9 g, 0.051 mol, 4.1 ml). The mixture was heated under reflux for 2 h, until little hydrogen chloride was evolved. The solution was allowed to cool to room temperature, filtered and extracted with five 20 ml portions of 12 *N* hydrochloric acid. The extract was diluted with 4 volumes of water and adjusted to *pH* 6–7 with ammonium hydroxide. The product was removed by filtration, washed with water and air dried. A yield of 5.2 g (85%) of compound was obtained, m.p. 132–134°C. A sample crystallized from ethanol melted at 137–139°C (Lit. [13] m.p. 137–139°C, yield 43%).

B. To 8-nitroquinoline (10.4 g, 0.06 mol) dissolved in acetic acid (120 ml) at near boiling was added *NCS* (8.8 g, 0.066 mol) in small portions with stirring over 1 h. The solution was brought to boiling and allowed to stir for 2 h without further heating. It was monitored by gas chromatography to make sure that all of the starting material had reacted, after which it was poured into 500 ml of water and stirred for 0.5 h. The solids were removed by filtration, washed with water and air dried. The yield of product was 12 g (96%), m.p. 128–130°C.

Crystallization from ethanol raised the melting point to 137–138°C.

^{1}H-NMR: $\delta = 9.05$ (d, 2-H), 8.75 (d, 4-H), 8.33 (q, 7-H), 8.25 (q, 5-H), 7.86 (q, 6-H), $J_{2,4} = 3$ Hz, $J_{5,6} = 7$ Hz, $J_{5,7} = 1.5$ Hz, $J_{6,7} = 8$ Hz.

3-Bromo-8-nitroquinoline

The title compound was obtained from 8-nitroquinoline and *NBS* in acetic acid in the same manner as 3-chloro-8-nitroquinoline was prepared by chlorination with *NCS*. The yield of product was nearly quantitative, m.p. 115–117°C. Two recrystallizations from ethanol raised the melting point to 122–123°C (Lit. [14] m.p. 123°C, yield 55%).

^{1}H-NMR: $\delta = 9.25$ (d, 2-H), 9.03 (d, 4-H), 8.46 (q, 7-H), 8.39 (q, 5-H), 7.94 (q, 6-H), $J_{2,4} = 2$ Hz, $J_{5,6} = 7$ Hz, $J_{5,7} = 1.5$ Hz, $J_{6,7} = 8$ Hz.

8-Amino-3-chloroquinoline

3-Chloro-8-nitroquinoline (27.6 g, 0.13 mol) dissolved in 100 ml of methanol was shaken in a Parr hydrogenator in the presence of 2 g of 10% palladium on carbon under 3 atmospheres of hydrogen. After the theoretical amount of hydrogen was taken up, the catalyst was removed by filtration, and the solvent was evaporated under reduced pressure. The residue weighed 23.5 g (nearly quantitative), m.p. 98–103°C. The product was purified by steam distillation and crystallization from ethanol, m.p. 104°C (Lit. [13] m.p. 105°C, yield 77%).

^{1}H-NMR: $\delta = 8.68$ (d, 2-H), 8.34 (d, 4-H), 7.37 (q, 6-H), 7.06 (q, 5-H), 6.86 (q, 7-H), 6.02 (broad s, H-NH_2), $J_{2,4} = 2.5$ Hz, $J_{5,6} = 8$ Hz, $J_{6,7} = 7$ Hz.

8-Amino-3-bromoquinoline

The title compound was prepared in 92% yield in the same manner as 8-amino-3-chloroquinoline, m.p. 106–107°C (Lit. [14] m.p. 106–107°C, yield 77%).

^{1}H-NMR: $\delta = 8.85$ (d, 2-H), 8.57 (d, 4-H), 7.46 (q, 6-H), 7.13 (q, 5-H), 7.06 (q, 7-H), 6.10 (broad s, H-NH_2), $J_{2,4} = 2$ Hz, $J_{5,6} = 8$ Hz, $J_{5,7} = 1.5$ Hz, $J_{6,7} = 7$ Hz.

3-Chloro-8-quinolinol

A mixture of 8-Amino-3-chloroquinoline (8.0 g, 0.044 mol) in water (21 ml) and sulfuric acid (14 ml) was prepared in a 100 ml glass jar and sealed in a 400 ml monel pressure vessel containing a small amount of water. After heating at 220°C for 15 h, the vessel was cooled, and the contents were adjusted to *pH* 6 with ammonium hydroxide then subjected to steam distillation. The product was removed from the distillate by filtration and air dried. The yield of compound was 7.5 g (93%), m.p. 105–106°C. A sample crystallized from aqueous ethanol melted at 108°C (Lit [9] m.p. 108–109°C, yield 5%).

3-Bromo-8-quinolinol

The title compound was prepared from 8-amino-3-bromoquinoline as 3-chloro-8-quinolinol was. The yield of product was 86%, m.p. 111.5–112.5°C (Lit [15] m.p. 111°C, yield 62%).

4-Chloro-8-methoxyquinoline

A mixture of 4-hydroxy-8-methoxyquinoline [16] (50 g, 0.29 mol) and 500 ml of phosphorus oxychloride was heated under reflux with stirring for 3 h and allowed to cool with continued stirring overnight. The excess phosphorus oxychloride was recovered in a rotary evaporator, and the residue was transferred to an ice-water slurry which was adjusted to *pH* 6–7 with ammonium hydroxide. The compound was removed by filtration, washed with water, and dried in air. The yield was 53 g (95%), m.p. 78–79°C (Lit. [16] m.p. 79–80°C, yield 78%).

^{1}H-NMR: $\delta = 8.91$ (d, 2-H), 7.86 (d, 3-H), 7.80 (q, 5-H), 7.76 (q, 7-H), 7.41 (q, 6-H), 4.10 (s, H$-$$OCH_3$), $J_{2,3} = 4.5$ Hz, $J_{5,6} = 7$ Hz, $J_{5,7} = 1.5$ Hz, $J_{6,7} = 8$ Hz.

4-Bromo-8-methoxyquinoline

4-Hydroxy-8-methoxyquinoline (7.0 g, 0.04 mol) was added in portions with stirring to a solution of phosphorus oxybromide (28 g, 0.1 mol; 10 ml) in 40 ml of chloroform. The mixture was heated under reflux for 4 h and poured into an ice-water slurry then stirred to decompose the excess phosphorous oxybromide. The chloroform layer was separated and the aqueous layer was adjusted to *pH* 6–7 with ammonium hydroxide and extracted with additional chloroform. The combined chloroform solutions were washed with water and decolorized with carbon. The solvent was evaporated under vacuum leaving a residue of 8.3 g (87%) of product, m.p. 96–97°C. Recrystallization from ethanol did not change the melting point (Lit. [15] m. p. 86–87°C, yield not given).

^{1}H-NMR: $\delta = 8.84$ (d, 2-H), 8.07 (d, 3-H), 7.81 (q, 5-H), 7.76 (q, 7-H), 7.42 (q, 6-H), 4.12 (s, H-OCH_3), $J_{2,3} = 5$ Hz, , $J_{5,6} = 5$ Hz, $J_{5,7} = 2$ Hz, $J_{6,7} = 8$ Hz.

4-Chloro-8-quinolinol

The title compound was prepared by hydrolysis of 4-chloro-8-methoxyquinoline in 76% sulfuric acid in the proportion of 1 g of methoxy compound to 8 ml of acid as previously published [17]. The yield of product was 89%, m.p. 139–141°C. Purification was by steam distillation followed by air drying, m.p. 145–146°C (Lit. [17] m.p. 141–143°C, yield 88%; [18] m.p. 145–146°C, yield 78%).

4-Bromo-8-quinolinol

The title compound was prepared in 92% yield from 4-bromo-8-methoxyquinoline in the same manner as 4-chloro-8-quinolinol, m.p. 136–138°C. It was steam distilled and air dried, m.p. 141–142.5°C (Lit. [15] m.p. 134–135°C, yield 53%).

2-Acetamido-5-chlorophenyl Acetate

This compound was prepared previously [21].

^{1}H-NMR: $\delta = 9.60$ (s, H-NH), 8.03 (q, 3-H), 7.40 (d, 6-H), 7.34 (q, 4-H), 2.34 (s, CH_3 of $-OCOCH_3$), 2.12 (s, CH_3 of $-NHCOCH_3$), $J_{3,4} = 8$ Hz.

6-Chloro-8-quinolinol

A mixure of 2-acetamido-5-chlorophenyl acetate (40 g, 0.18 mol), glycerol (50 g, 0.54 mol), arsenic oxide (30 g, 0.13 mol), and sulfuric acid (30 ml) was heated under reflux for 3 h. The reaction mixture was cooled and poured into 500 ml of water, made neutral with ammonium hydroxide, and steam distilled. The compound was filtered and air dried (46%), m.p. 142°C. A sample crystallized from ethanol melted at 144°C (Lit. [19] m.p. 144°C, yield 42–49%).

2-Acetamido-5-bromophenyl Acetate

A mixture of 2-acetamidophenyl acetate [21] (5.8 g, 0.03 mol), *NBS* (5.3 g, 0.03 mol) in 75 ml of acetic acid was stirred at ambient temperatures overnight. The mixture was poured into 800 ml of water and stirred an additional 0.5 h, after which the product was removed by filtration, washed with water and dried in air. The yield of compound was 5.5 g (67%), m.p. 156–158°C. A sample obtained after dissolution in aqueous ethanol followed by decolorization with carbon melted at 163–164°C (Lit. [22] m.p. 128°C, [23] m.p. 125°C, yield 74%).

Anal. calcd. for $C_{10}H_{10}BrNO_3$: C 44.13, H 3.71, Br 29.37, N 5.15. Found: C 44.00, H 3.72, Br 29.00, N 5.00. ^{1}H-NMR: $\delta = 9.56$ (s, H of $-NH$), 7.97 (q, 3-H), 7.51 (d, 6-H), 7.45 (q, 4-H), 2.32 (s, CH_3 of $-OCOCH_3$), 2.09 (s, CH_3 of $-NHCOCH_3$), $J_{3,4} = 8$ Hz.

6-Bromo-8-quinolinol

This compound was prepared from 2-acetamido-5-bromophenyl acetate in the same manner as for 6-chloro-8-quinolinol. The yield of product was 33%, m.p. 143–145°C (Lit. [15] m.p. 138–139°C, yield nor reported).

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