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First Safe and Practical Synthesis of 2-Amino-8-hydroxyquinoline

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Abstract:

The first safe and efficient synthesis of the important building block 2-amino-8-hydroxyquinoline (1) is described. Starting from the readily available *N*-oxide 3 of the cheap bulk chemical 8-hydroxyquinoline (2), the target compound is obtained in a two-step one pot procedure in good overall yield (53−66%) and purity (>98%) on a kilogram scale without chromatography.

Introduction

Aminoquinolines are important constituents in a variety of pharmaceutically important compound classes, most notably perhaps the antimalarials quinine, chloroquine, and their derivatives.[1] Recently, *N*-acylated and *N*/*O*-alkylated derivatives of 2-amino-8-hydroxyquinoline (**1**) have become of interest as NO-synthase inhibitors,[2] peptide deformylase inhibitors,[3] 5-HT2C receptor agonists,[4] heparanase inhibitors,[5] tyrosine kinase inhibitors,[6] and antiviral agents.[7] They have also been proposed as chemoluminescent probes for the analytical determination of lanthanides[8] and materials for second-order nonlinear optical applications.[9]

For a development program, we needed an expedient, scaleable synthesis of **1**. We were surprised to learn that among the 25 literature references currently found for this compound in *Chemical Abstracts*,[10] not a single one is listed for its preparation. Closer scrutiny revealed a 1936 patent[11] covering the synthesis of **1** via *Chichibabin* reaction[12] of 8-hydroxyquinoline and a 1956 Grace & Co. patent[13] claiming chloramine amination of 8-hydroxyquinoline as a process for the preparation of **1**. While the latter was not investigated further due to the well-known hazardous nature of chloramine,[13] initial attempts to reproduce the *Chichibabin*-patent[11] procedure were disappointing.[14]

Although an alternative synthesis via a 2-chloroquinoline derivative appeared feasible,[15] starting materials for this approach are expensive and not readily commercially available. A market analysis of related quinoline building blocks revealed that 8-hydroxyquinoline is by far the most convenient starting material.[16] There is only scarce literature precedence for the direct conversion of quinoline-*N*-oxides to the corresponding 2-aminoquinolines,[17,18] whereas the same transformation of hydroxyquinoline-*N*-oxides has not

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(12) Chichibabin, A. E.; Seide, O. A. *J. Russ. Phys. Chem. Soc.* **1914**, *40*, 1216.
(13) Rudner, B. (W. R. Grace & Co.). U.S. Patent 2,892,841, 1956. Chloramine [chloramide] is a toxic, strong lachrymator/irritant. It is instable and highly explosive in the liquid state and currently not produced commercially in the United States; see: *Dangerous Properties of Industrial Materials Report* **1993**, *13*, 502. For a review of the chemical properties of chloramine, see: Sisler, H. H. *J. Chem. Educ.* **1983**, *60*, 1002.
(14) Van Eijk, A. (ChemShop B.V., Netherlands) and Roeder, M. (CarboGen, Switzerland), unpublished results. The procedure was found to give multiple products, also in the case of the *O*-methylated derivative, and regularly led to tar formation. Moreover, a strongly exothermic behaviour was observed in the small-scale experiments that suggested a potential for thermal runaway on larger scale. Reports on the *Chichibabin* reaction of quinolines are scarce in the literature: the reaction mechanism appears to be complex and has been shown to lead to, among other products, 3,4-dihydroquinolines and the 4-amino regioisomer; see: Tondys, H.; Van der Plas, H. C.; Wozniak, M. *J. Heterocycl. Chem.* **1985**, *22*, 353 and Kametani, T.; Kigasawa, K.; Iwabuchi, Y.; Hayasaka, T. *J. Heterocycl. Chem.* **1965**, *2*, 330. *Chichibabin* reactions of hydroxyquinolines have not been reported to date (SciFinder/Beilstein Searches, Feb 2004).
(15) See, for instance: Gershon, H.; Clarke, D. D. *Monatsh. Chem.* **1991**, *122*, 935. Note that transient *O*-protection of the 8-hydroxy group would be required for these approaches, thus lengthening the synthetic sequence by two steps.
(16) In small quantities, 2-amino-8-hydroxyquinoline (**1**) can be purchased from Fluka/Sigma, but we were unable to identify a bulk manufacturer. 2,8-Dihydroxyquinoline as well as 2-chloro-8-hydroxy(or methoxy)quinoline are either very expensive or not commercially available beyond gram quantities. On the other hand, 8-hydroxyquinoline is offered on a multi-kilogram scale by a variety of bulk manufacturers (<$50/kg).
(17) Only two reports on the direct conversion of a quinoline-*N*-oxide to the corresponding 2-aminoquinoline were found: Miura, Y.; Takaku, S.; Fujimura, Y.; Hamana, M. *Heterocycles* **1992**, *34*, 1055 and Glennon, R. A.; Slusher, R. M.; Lyon, R. A.; Titeler, M.; McKenney, J. D. *J. Med. Chem.* **1986**, *29*, 2375 (both use $TsCl/NH_3$).
(18) Even for the conversion of pyridine-*N*-oxides to the corresponding 2-aminopyridine there is surprisingly little precedence: a Bayer patent (Rivadeneira, E.; Jelich, K. DE 4232175, 1992) claims a process for 2-amino-5-methylpyridine via HBr-dealkylation of the 2-trimethylammonium pyridine salt, obtained by reaction of the pyridine-*N*-oxide with NMe_3. A Lonza patent (EP 090173, 1983) claims the synthesis of 2-aminopyridines via decarboxylative α-amination of the corresponding 2-carboxypyridine-*N*-oxides. A prior reference (Wachi, K.; Terada, A. *Chem. Pharm. Bull.* **1980**, *28*, 465) mentions the use of a not readily accessible activating agent (4-chloro-2,2-dimethyl-2H-1,3-benzoxazine) for the conversion of pyridine-*N*-oxide to 2-aminopyridine.

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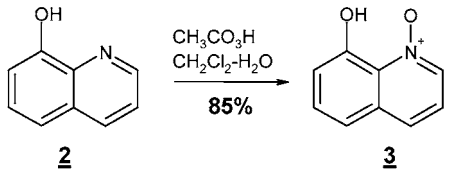
Scheme 1



been reported.[10] Our goal was to find reaction conditions for the direct conversion of 8-hydroxyquinoline-*N*-oxide (**3**) to the 2-amino compound (**1**) in high yield and regioselectivity, while eliminating the need for protecting the 8-hydroxy group.

Results and Discussion

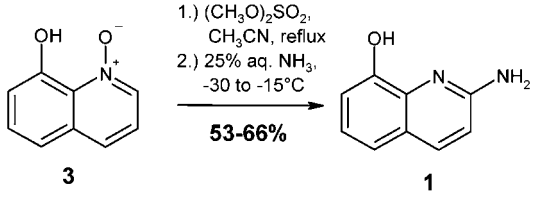
8-Hydroxyquinoline-*N*-oxide (**3**) is readily available from 8-hydroxyquinoline (**2**); for our purposes, we developed an improved variant of the original peracetic acid oxidation protocol of Khaletskii et al.[19] (Scheme 1).

Different activating agents were then screened with **3** (*methyl iodide in dichloromethane, ethyl chloroformate in tetrahydrofuran, trimethylsilyl triflate in acetonitrile or dichloromethane, and dimethyl sulfate in toluene, acetonitrile or chlorobenzene, data not shown*), followed by quenching the reaction with solutions of ammonia in different solvents. Of the activating agents tested, only dimethyl sulfate resulted in notable conversion yields with acetonitrile as the reaction solvent being superior to chlorobenzene and toluene (*homogeneous reaction!*).[20]

The subsequent quench reaction with ammonia was investigated in different solvents: in dioxane, a multicomponent mixture resulted, whereas in methanol, considerable amounts of a methoxy-substituted quinoline were observed. The best results were obtained using aqueous ammonia at low temperatures. For thermal safety reasons, the quench was performed in "inverse mode", by slowly adding a solution of the *O*-methylated intermediate to cooled aqueous ammonia. For correctly estimating reaction turnover, it proved essential to monitor both reaction steps by HPLC, as TLC-monitoring initially gave inconsistent readings on reaction progress.

The yield for the two step-process in small-scale development experiments varied between 34 and 66%; the two demonstration runs for the production campaign gave crude product yields of 53−66% with an HPLC-purity of 91−93% (Scheme 2). The 3-kg production was run under identical conditions and resulted in a 59% crude yield of **1** with an HPLC purity of 90.3%. The purity could be improved to 99.5% by filtration over a silica gel plug and subsequent

Scheme 2



crystallization. The yield of 99.5% pure product was 47.6% over two steps,

Conclusions

In summary, a robust three step-process (two steps, "one-pot") for kilogram-scale, chromatography-free preparation of 2-amino-8-hydroxyquinoline (**1**) in high purity (≥98%) was developed from an economic and readily available starting material (*8-hydroxyquinoline*). The transformation of the quinoline-*O*-methyl-*N*-oxide salt to the corresponding 2-aminoquinoline is novel and might well prove useful for the practical synthesis of other 2-aminoquinolines.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers (Aldrich/Fluka) and were used without further purification. All the melting points are uncorrected and were determined on a Buchi apparatus. ^{1}H NMR spectra were recorded at 400 or 500 MHz on a Bruker DPX 400/500 instrument and interpreted first order. ^{13}C NMR spectra were recorded at 100 or 125 MHz on a Bruker DPX 400/500 instrument. Chemical shifts are expressed in ppm using the solvent signal as internal reference. Assignments are based on heteronuclear 2D-NOESY experiments. IR spectra were measured on a BioRad FTS-3000-MX FT-spectrometer. Mass spectra were recorded on a Finnigan LCQ-Duo ion trap, APCI positive. Exact mass determinations were performed on a Micromass QtoF Ultima API instrument (a solution of 0.1% caffeine was used for lock mass correction). HPLC-method used for purity determinations and in-process-controls (IPC): YMC-Column (RP-18), 250 mm × 4.6 mm, particle size 5 μ, mobile phase A: 0.1% TFA in H_2O, mobile phase B: 0.1% TFA in acetonitrile; gradient: 0 min 95% A, 5% B, 20 min 30% A 70% B; flow 1 mL/min; temperature 25 °C; detection wavelength: 250 nm, retention time: 8-hydroxyquinoline-*N*-oxide (**3**): 13.3 min; 2-amino-8-hydroxyquinoline (**1**): 9.26 min.

8-Hydroxyquinoline-*N*-oxide (3). To a solution of 8-hydroxyquinoline (**2**) (212.16 g, 1.46 mol) in CH_2Cl_2 (2200 mL) a dilute solution of peracetic acid (∼39% w/w in aqueous acetic acid, 310 mL, 1.79 mol, 1.2 equiv) was added dropwise at 6 °C. The solution was stirred at room temperature for an additional 3 h before the reaction was quenched by the careful addition of a solution of sodium pyrosulfite (55.13 g, 0.29 mol, 0.2 equiv) in water (90 mL). Successive extraction of the organic phase with 1 M HCl (2 × 750 mL), saturated aqueous $NaHCO_3$ (850 mL), saturated aqueous Na_2CO_3 (130 mL) (to adjust the pH to 8), and brine (400 mL), followed by evaporation of the organic phase under reduced pressure gave the crude product, which was taken up in water

(19) On a gram scale, the *N*-oxide **3** is commercially available from several suppliers. Various oxidation systems have been used for the selective *N*-oxidation of 8-hydroxyquinoline: (a) peracetic acid (Khaletskii, A. M.; Pesin, V. G.; Tsin, C. *Zh. Obsh. Khim*. **1958**, *28*, 2348 [only 20% yield]). (b) H_2O_2 (Rao, A. V. R.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065 and Chauhan, S. M. S.; Kalra, B.; Mohapatra, P. P. *J. Mol. Catal. A: Chem.* **1999**, *137*, 85). (c)) MCPBA (Shrader, W. D.; Celebuski, J.; Kline, S. J.; Johnson, D. *Tetrahedron Lett.* **1988**, *29*, 1351). (d) O_2/2-methylpropanal (Dongre, R. S.; Rao, T. V.; Sharma, B. K.; Sain, B.; Bhatia, V. K. *Synth. Commun*. **2001**, *31*, 167).

(20) The methylation of **3** has been reported (by dimethyl sulfate: [19b], by methyl mesylate: [19c]).

(500 mL), stirred for 30 min at room temperature, and filtered. The wet cake was stripped with toluene (500 mL) under vacuum to give **3** as a yellow solid (198.89 g, 84.5% yield), HPLC-purity: 97.1A%. Mp 137 °C. DSC: mp 139.5 °C, single peak [Aldrich material: 138−139 °C], exotherm observed at T_{onset} 259 °C (764 J/g). MS: 162.1 [MH^+], 146.1. ^{1}H NMR (400 MHz, DMSO): δ 15.51 (s, 1H), 8.54 (d, 1H), 8.09 (d, 1H), 7.58−7.48 (m, 2H), 7.43 (d, 1H), 7.10 (d, 1H). ^{13}C NMR (100 MHz, DMSO): δ 153.3, 135.3, 132.0, 130.3, 130.1, 128.7, 121.7, 117.0, 113.9.

2-Amino-8-hydroxyquinoline (1). [*95-g Pilot Experiment*]. A suspension of 8-hydroxyquinoline-*N*-oxide (**3**) (95.0 g, 0.581 mol (corrected for 98.5% NMR assay), 1.0 equiv) in 200 mL of acetonitrile was heated to reflux (→ clear, light-brown solution). Dimethyl sulfate (58.1 mL, 0.606 mol, 1.05 equiv) was added slowly over a 55-min period at 77−81 °C. The reaction was monitored by HPLC (see method above). After 3.5 h, IPC indicated ~80% conversion. After 5 h an additional portion of dimethyl sulfate (15 mL, 0.158 mol, 0.26 equiv) was added over a 25-min interval. Approximately 40 min later, IPC showed 90% conversion. (The *O*-methylated **3** was not isolated. For safety reasons, a DSC was measured of a mixture of **3** and 1.1 equiv of dimethyl sulfate in acetonitrile. It indicated only a mild exotherm (67.5 J/g) at T_{onset} = 151 °C.) After 11 h of reflux, stirring was continued at ambient temperature overnight. The reaction mixture was slowly added to a precooled solution of aqueous ammonia (25% w/w, 130 mL) at −20 °C over a 1 h period. After an additional 10 min of stirring at −25 °C, more aqueous ammonia (25%, 40 mL) was added. Stirring was continued at −10 °C for 1.5 h before the suspension was filtered. The filter cake was washed with 2 × 120 mL of H_2O/CH_3CN (1:1). Drying of the filter cake at 50 °C/10 mbar afforded the crude product as a brown solid (49.8 g, 53.5%, 91.0A% HPLC). The solid was suspended in CH_3CN (1400 mL), stirred at 40 °C for 5 h and at ambient temperature for an additional 12 h. Plug filtration over 250 g of silica gel (washed with 4 × 500 mL CH_3CN) and evaporation of the filtrate under reduced pressure gave a beige-brown solid (43.7 g, 47.0%, 92.0A% HPLC). For spectroscopic characterization, an aliquot of this product (10.06 g) was purified further as follows: the sample was suspended in CH_3CN (20 mL), stirred at 60 °C for 30 min, cooled to ambient temperature, then kept at 0−4 °C for 72 h. Filtration of the precipitated crystals, washing with cold (−10 °C) CH_2Cl_2 (2 × 5 mL), and drying in a vacuum oven yielded 8.78 g (87.3%) slightly beige, crystalline **1** (99.0A% HPLC).

[*3-kg Production Run*]. A suspension of 8-hydroxyquinoline-*N*-oxide (**3**) (2.997 kg, 18.43 mol corr. for 99.11% assay content) in CH_3CN (5.5 l) was heated to reflux (→ dark-brown solution). Dimethyl sulfate (2.557 kg, 20.27 mol, 1.1 equiv) was added at 79−82 °C over a 45-min period. The addition funnel was rinsed with CH_3CN (0.65 l). After 4 h, IPC #1 indicated approximately 73% conversion. After a total of 11 h at reflux (~85 °C), the reaction mixture was allowed to reach ambient temperature overnight. IPC #2 after 12 h showed 85% conversion. The reaction mixture was slowly added to a reactor containing precooled (−30 °C) aqueous ammonia (25% w/w, 4.0 L), such that the internal temperature did not exceed −15 °C (~1 h and 45 min addition time). After an additional 1.5 h stirring at −15 °C, the suspension was filtered (~35 min filtration time). The filter cake was washed with cold (−15 °C) CH_3CN (2 × 1.8 l) and chilled (0−4 °C) water (2.45 l). The filter cake was blow-dried with nitrogen overnight at ambient temperature and further dried at 45−50 °C under vacuum. The crude product was obtained as a beige-brown solid (1.748 kg, 59.2% yield, 90.3A% HPLC). This solid was dissolved in CH_3CN (53.5l) and suction-filtered over silica gel (7.5 kg, soaked with CH_3CN). After rinsing the filter bed with CH_3CN (46 l total), the solvent was evaporated under reduced pressure to a residual volume of approx 3−4 L (4.405 kg), yielding a crystal slurry, which was cooled to 0−3 °C and filtered. The filter cake was rinsed with chilled (−15 °C) CH_3CN (1 L) and blow-dried with nitrogen. Further drying at 45 °C/vacuum afforded crystalline **1** as a pale-amber solid (1.405 kg, 47.6% yield, 99.5A% HPLC). DSC: mp 156.7 °C (Fluka material: 157−160 °C. [The two patent references[11,13] give a melting point of 60−63 °C as the only phyical data for **1**. In the absence of any spectroscopic analysis, and since the difference to the true melting point is ~100 °C, it may be doubted whether the two patent procedures succeeded in the synthesis of **1**.]), single peak, no exotherm observed up to 270 °C. ^{1}H NMR (500 MHz, DMSO): δ 6.4 (br s, 2H, N*H*$_2$); 6.80 (d, 1H, *H*-C(3), $^3J_{3,4}$ = 8.6 Hz); 6.88 (d, 1H, *H*-C(7), $^3J_{6,7}$ = 7.1 Hz); 7.00 (t, 1H, *H*-C(6), $^3J_{6,7} \approx {}^3J_{6,5}$ = 7.1 Hz); 7.10 (d, 1H, *H*-C(5), $^3J_{5,6}$ = 7.9 Hz); 7.87 (d, 1H, *H*-C(4), $^3J_{4,3}$ = 8.6 Hz); 8.45 (br s, 1H, O*H*) [On the basis of the coupling constants observed between *H*-C(3) and *H*-C(4) (8.6 Hz), the *2-amino* substitution in **1** could be assigned unambiguously, since the $^3J_{H,H}$-coupling constants in substituted pyridines are known to be quite different: typical $^3J_{2,3}$ = 4−6 Hz, whereas typical $^3J_{3,4}$ = 7−9 Hz.[21] By the same token, regioselectivity of the ammonia addition is unknown for the patent syntheses.[11,13]]. ^{13}C NMR (125 MHz, DMSO): δ 110.5, 112.8, 117.6, 121.5, 122.8, 137.1, 137.4, 150.0, 157.0. IR (KBr, cm^{-1}): 3403m, 3308m/br, 1632s, 1577s, 1514s, 1487s, 1439s, 1387s, 1357s, 1299s, 1269s, 1238s, 1196s, 1147s, 1078s, 1048m, 982m, 951m, 930m, 880s, 835m, 803sh, 742s, 712m. HR-MS: exact mass calculated for $C_9H_8N_2O$: 160.0637, M + H^+ = 161.0715; observed mass: 161.0658 (M + H^+).

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Note Added after ASAP Publication: There was an error in the address for the authors from Switzerland in the version published on the Web June 25, 2004. The version published July 1, 2004, and the print version are correct.

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