Benzo[*f*]quinoline: Synthesis and Structural Analysis

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*We report an improved method of synthesis and a detailed spectral study (^{1}H-, and ^{13}C- NMR, MS) for benzo[f]quinoline **2**. We also prepared benzo[f]quinoline hydrochloride **1** and fully characterized it. A comparative NMR analysis has been done, indicating clear differences between **2** and **1**, in terms of chemical shifts and coupling, according to their relative position to nitrogen respectively nitrogen hydrochloride atoms. The MS spectrum for benzo[f]quinoline is a typical and characteristic example of fragmentation for a nitrogen heterocycle.*

Keywords: benzo[f]quinoline, benzo[f]quinoline hydrochloride, synthesis, NMR, mass spectra

Benzo[f]quinoline derivatives are interesting N-heterocyclic systems, structurally analogous to the steroid skeleton [1-3]. In continuing our work to synthetise tetracyclic nitrogen heterocyclic systems structurally analogous to the naturally steroids [1-3], we decided to use benzo[*f*]quinoline as starting material. A literature search showed as that the best method in terms of yields and simplicity was described in [4]. They claim a yield of 81.5% and recrystallization from alcohol-water mixture in order to obtain the pure compound. We repeated exactly the work-up procedure, several times, but the results were not as described. After recrystallization from alcohol-water the yield in benzo[*f*]quinoline was around 1%. Even for a Skraup synthesis this yield is rather low.

The emphasis of this work was to find an improved method for the synthesis of benzo[*f*]quinoline and to perform a detailed spectral study (^{1}H-, and ^{13}C- NMR, MS) for this compound. In equal measure we were interested to prepare benzo[*f*]quinoline hydrochloride and to characterize it, having in view its potential biological activity.

Experimental part

The ^{1}H- and ^{13}C-NMR spectra and two-dimensional 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) experiments were recorded on a Bruker Avance 400 DRX spectrometer operating at 400/100 MHz. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. GCMS was performed using a Shimadzu GCMS-QP2010. The instrument uses a quadrupole mass spectrometer and detects samples via electron impact ionization (EI) or chemical ionization using methane (CI). Melting points were determined on a MELTEMP II apparatus and are uncorrected.

General procedure for syntheses

A suspension of 100 g of arsenic acid and 100 g of 2-naphthylamine in 215 g of glycerol was heated at 140° while well stirred. About one-half of 200 g of conc. sulfuric acid was added in large portions and the remainder dropwise after the solid (which first had formed) had dissolved. The mixture was refluxed at 150 -155° for 4 h , poured into 2 L of water, allowed to stand overnight and filtered. The filtrate was neutralized by dropwise addition of 6 *N* sodium hydroxide with extremely rapid mechanical agitation (to *p*H 9). The crystalline mass was filtered off, dried and dissolved in acetone. The benzo[f]quinoline hydrochloride was precipitated by saturating the solution with dry hydrogen chloride (the hydrogen chloride was obtained by dropping slowly sulfuric acid on sodium chloride). When benzo[*f*]quinoline hydrochloride is desired, the product is filtered off by suction, washed thoroughly three times with cold water and, then dried when a dark green solid is obtained. No other purification is required. When benzo[*f*]quinoline is need, the benzo[*f*]quinoline hydrochloride is filtered off, dissolved in hot water, treated with charcoal, filtered, and the free base was again precipitated by neutralizing with 6 *N* sodium hydroxide. The crude benzo[*f*]quinoline is a reddish solid, obtained in 10% yield. The pure compound is obtained by flash chromatography (silica gel, dichloro-methane/methanol: 99.5/0.5) affording a white powder in 6% yield. (Clem et al. claimed that the crude product was recrystallized from alcohol-water mixture when benzo[*f*]quinoline was obtained in a yield of 81.5%, mp 93° C).

Benzo[*f*]quinoline hydrochloride, 1. Dark green solid, (31%), mp >360° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.96-7.87 (2H: H_6,H_7, m, $J_{6,5}$= 8 Hz, $J_{7,8}$= 8.4 Hz), 8.24-8.17 (2H: H_3,H_8, m, $J_{3,2}$= 8.4 Hz, $J_{3,4}$= 5.2 Hz, $J_{8,7}$= 8.4 Hz), 8.30-8.27 (1H: H_9, d, $J_{9,10}$= 9.2 Hz), 8.51-8.49 (1H: H_{10}, d, $J_{10,9}$= 9.2 Hz), 9.04-9.02 (1H: H_5, d, $J_{5,6}$= 8 Hz), 9.26-9.25 (1H: H_4, dd, $J_{4,3}$= 5.2 Hz), 9.94-9.91 (1H: H_2, d, $J_{2,3}$= 8.4 Hz). ^{13}C-NMR ($CDCl_3$, δ, ppm): 119.48 (C_9), 122.81 (C_8), 123.87 (C_5), 126.70 (C_{4a}), 127.94 (C_{4b}), 129.26 (C_6, C_7), 129.41 (C_3), 131.28 (C_{8a}), 135.91 (C_{10}), 139.73 (C_2), 139.99 (C_{10a}), 143.56 (C_4).

Benzo[*f*]quinoline, 2. White powder, (6%), m p 91-92° C. ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.52-7.48 (1H: H_3, q, $J_{3,2}$= 4.4 Hz, $J_{3,4}$= 8.4 Hz), 7.67-7.59 (2H: H_6,H_7, m, $J_{6,5}$= 8.4 Hz, $J_{7,8}$= 9.2 Hz), 7.99-7.88 (3H: H_{10},H_9,H_8, m, $J_{8,7}$= 9.2 Hz), 8.56-8.54 (1H: H_5, d, $J_{5,6}$ = 8.4 Hz), 8.89-8.86 (1H: H_4, dd, $J_{4,3}$= 8.4 Hz), 8.94-8.93 (1H: H_2, dd, $J_{2,3}$= 4.4 Hz). ^{13}C-NMR ($CDCl_3$, δ, ppm): 121.21 (C_9), 122.49 (C_8), 125.34 (C_{4a}), 127.02 (C_5), 127.25 (C_6), 128.03 (C_7), 128.62 (C_3), 129.52 (C_{8a}), 130.64 (C_2), 130.82 (C_{10}), 131.58 (C_{4b}), 148.05 (C_{10a}), 149.55 (C_4). MS (m/z, %): 179 (M^+, BP, 100%), 180 (17, $[M+1]^+$), 178 (23, $[M-1]^+$), 151 (62), 90 (24), 76 (58), 62 (16), 51 (20).

Results and discussion

In order to improve the method described [4], we use a mixture of 2-naphthylamine, glycerol, concentrated sulfuric acid, and arsenic acid (used as a powerful oxidation agent) are reacting via a Skraup synthesis. Initially benzo[*f*]quinoline hydrochloride **1** is obtained, which in alkaline media affords benzo[*f*]quinoline **2** (scheme 1).

Clem's work-up procedure is correct until the free base benzo[*f*]quinoline **2** is precipitated (by neutralizing with 6

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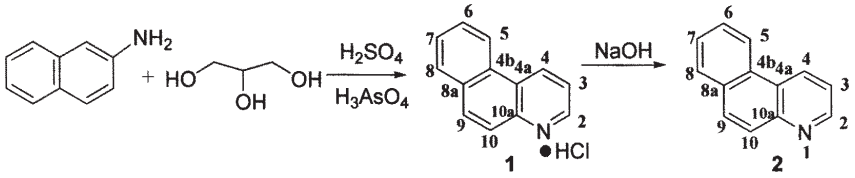


Scheme 1. Reaction pathway to obtain benzo[*f*]quinoline and benzo[*f*]quinoline hydrochloride

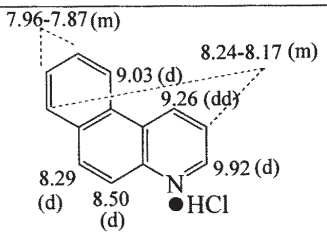
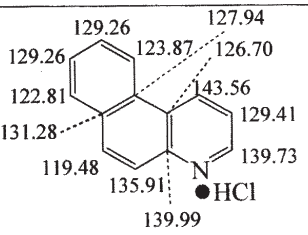
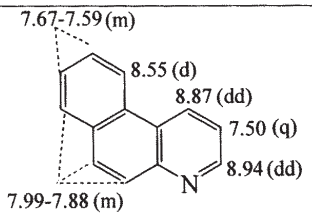
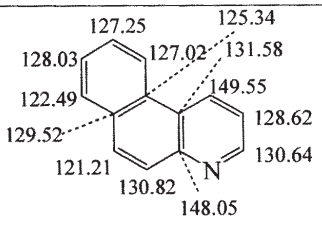
NMR/ comp.	^{1}H-NMR	^{13}C-NMR
1		
2		

Table 1
^{1}H-, AND ^{13}C- NMR DATA FOR BENZO[*f*]QUINOLINE AND BENZO[*f*]QUINOLINE HYDROCHLORIDE

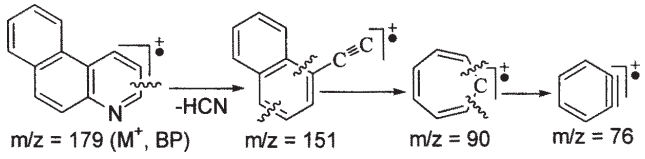
N sodium hydroxide); then the recommended procedure is described by us in the experimental part. When benzo[*f*]quinoline hydrochloride **1** is needed, one may follow also the experimental procedure described by us.

Because in the literature we did not find a detailed spectral study of benzo[*f*]quinoline **2** and benzo[*f*]quinoline hydrochloride **1** (^{1}H-, and ^{13}C- NMR, MS), we decided to do it here. The complete ^{1}H- and ^{13}C- NMR spectral data for both compounds are listed in table 1.

As it can be seen from table 1, the comparative NMR analysis indicates clear differences between **1** and **2**, in terms of chemical shifts and spin coupling. The protons are much more deshielded in hydrochloride **1**, by almost 1 ppm in the pyridine moiety and by 0.5 ppm in both benzene rings. We also noticed differences between **1** and **2**, in terms of couplings for protons H_2 (d and dd respectively), H_3 (m and q respectively), H_9 (d and m respectively) and H_{10} (d and m respectively). In the carbon spectra the differences are more pronounced in the pyridine ring and fused benzene neighbouring ring, namely carbons C_2, C_4, C_{4a}, C_{10a}, C_{10} (with roughly 5 to10 ppm), differing chemical shifts according to their relative position to the nitrogen atom.

The MS spectra (electron impact), are a nice fragmentation example for a nitrogen heterocycle. The fragmentation pathway for benzo[*f*]quinoline **2** is presented in scheme 2.

The molecular ion appears at m/z 179, being at the same time the base peak and the parent peak. The $[M-1]^+$ and $[M+1]^+$ are present, with relatively low intensity (23% and 17% respectively). The molecular ion undergoes cleavage of C_{10a} - N and C_2 – C_3 bonds, leading to the key fragment m/z 151 [M-27 (HCN)]. Subsequent fragmentation of the latter ion yields the fragments from m/z 90 and, further m/z 76, 62 and 51, all characteristic for aromatic nitrogen heterocycles.



Scheme 2. The fragmentation pathway for benzo[*f*]quinoline

Conclusion

We present here an improved method for the synthesis of benzo[*f*]quinoline. After purification by flash chromatography, benzo[*f*]quinoline **2** was obtained as a white powder, mp 91-92°C, yield 6%. We also prepared benzo[*f*]quinoline hydrochloride **1** and fully characterized it. A detailed spectral study, ^{1}H-, ^{13}C- NMR and MS have been done for these compounds. The comparative NMR analysis indicates clear differences between **1** and **2**: the protons are much more deshielded in hydrochloride **1**, the couplings are different in the pyridine and fused benzene neighbouring rings. In the carbon ^{13}C-NMR spectra the differences are more pronounced for carbons C_2, C_4, C_{4a}, C_{10a}, C_{10} (in the pyridine and fused benzene neighbouring rings), according to their relative position to the nitrogen respectively nitrogen atom. The MS spectrum for benzo[*f*]quinoline is a nice fragmentation example for a nitrogen heterocycle.

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