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# Fluorinated Benzo[*h*]quinolines and Benzo[*f*]quinolines

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**Thirteen kinds of fluorinated derivatives of benzo[*h*]quinoline and benzo[*f*]quinoline were synthesized by means of the Schiemann reaction or Skraup reaction, or by an electrolytic method. The synthesized derivatives carry one or two fluorine atoms at the bay-region, the K-region, and/or on the pyridine moiety of the molecules. These compounds can be used as models to examine the effect upon genotoxicity of fluorine substitution at appropriate sites on aromatic rings. Physicochemical and spectroscopic data of the fluorinated derivatives are given.**

**Key words** benzoquinolines; fluorine substitution; electrochemical fluorination

A wide range of aromatic hydrocarbons undergo metabolic oxidation to form arene oxides, most of which have some ability to alkylate biological materials, such as cellular DNA, which may lead to mutagenesis and carcinogenesis. It is generally accepted that bay-region epoxides in a sterically hindered molecular environment exert potent genotoxicity.[1] As previously reported, quinoline, an aza-analogue of naphthalene, is potently mutagenic and carcinogenic in spite of its lack of a bay-region structure.[2] We proposed that quinoline might be metabolized to its 2,3-epoxide-1,4-hydrate form, which may be a type of ultimate genotoxic structure of *N*-containing heteroaromatics, as is the bay-region epoxide.[3,4] It is noteworthy that 3-fluoroquinoline is completely non-mutagenic, probably because the fluorine atom on the pyridine moiety interferes with the enzymatic oxidation leading to 2,3-epoxide formation.[4] In general, halogen substitution may interfere with the formation of arene oxides on the aromatic moiety on which the halogen atom is located.[5] This suggests that the mutagenic capacity of aromatic hydrocarbons may be modified by introducing a halogen atom at sites responsible for genotoxic activation and detoxication, thereby altering the genotoxicity of these compounds. Among the halogen atoms, fluorine seems to be most appropriate for structural modification of bioactive substances, since this atom has similar covalent and van der Waals radii to those of the hydrogen atom, which presumably accounts for its mimicking of hydrogen in interactions with biological molecules. In addition, substituted fluorines are highly stable to biotransformation, especially one electron-step biological oxidation, due to the high electronegativity.[6] In this connection, we have extended our studies on potentiation and inhibition of the genotoxicity of quinolines by fluorine substitution to benzoquinolines, which have another fused benzene ring, providing these molecules with a bay region. This paper describes the synthesis of fluorinated derivatives of benzo[*h*]quinoline (B[*h*]Q) and benzo[*f*]-quinoline (B[*f*]Q) for use as model compounds to study how genotoxicity can be modified by fluorine substitution at the bay-region, the K-region, or on the pyridine moiety of these molecules. To our knowledge, fluorinated derivatives of B[*h*]Q and B[*f*]Q have not previously been reported in the literature.

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## Results

**Schiemann Reactions Starting with the Corresponding Amino Derivatives** Schiemann reactions were carried out by treating aromatic amines with isoamyl nitrite and $HBF_4$, followed by pyrolysis to afford the corresponding fluorine derivatives. The amines, except for 3-amino-B[*h*]Q and 2-amino-B[*f*]Q, were synthesized by nitration of B[*h*]Q or B[*f*]Q, followed by catalytic hydrogenation. The Schiemann reaction may be used for a wide range of aromatic amines but the reaction yields are generally low. 7-F-B[*h*]Q, 7-F-B[*f*]Q, 10-F-B[*h*]Q, and 10-F-B[*f*]Q were obtained in 16, 22, 0.8 and 21% yields from the corresponding amines, respectively. The yield of 9-F-B[*h*]Q from the nitro derivative was 17%. 3-F-B[*h*]Q and 2-F-B[*f*]Q, in which the fluorine atom is located on the pyridine moiety, were synthesized by means of the same reaction from the corresponding amines in 57 and 49% yields, respectively.

**Skraup Reactions with Glycerol or Nitromalonaldehyde, Followed in Some Cases by Schiemann Reactions** 6-F-B[*h*]Q was synthesized by treating 1-amino-4-fluoronaphthalene with glycerol and sodium *m*-nitrobenzenesulfonate in 80% $H_2SO_4$ at 140 °C. 3,6-diF-B[*h*]Q was synthesized by treating 1-amino-4-fluoronaphthalene with sodium nitromalonaldehyde, followed by a modified Skraup reaction, as described for 3-nitro-B[*h*]Q[7] synthesis, and then by catalytic reduction to 3-amino-6-F-B[*h*]Q, which was converted to 3,6-diF-B[*h*]Q through the Schiemann reaction.

**Electrochemical Partial Fluorinations of B[*h*]Q and B[*f*]Q** Electrochemical fluorination is a useful synthetic tool, but has seldom been used for synthesis of fluorinated *N*-containing heteroaromatics.[8,9] Recently, two of the present authors (K.M. and H.K.) succeeded in partial fluorination of quinoline and isoquinoline. In the present study, B[*h*]Q and B[*f*]Q were subjected to electrochemical fluorination with $Et_4NF \cdot 4.45HF$ as the electrolyte at a constant electric potential of 2.5 V.[9] The electrolytic product was then treated in aqueous alkali at room temperature, and 5-F-B[*h*]Q, 5,6,-diF-B[*h*]Q and 7,10-diF-B[*h*]Q were isolated from B[*h*]Q in yields of 19%, 8% and 16%, respectively. Treatment of B[*f*]Q in the same manner afforded 7,10-diF-B[*f*]Q in 47% yield, together with benzo[*f*]quinoline-7,7,10,10-tetrafluoride

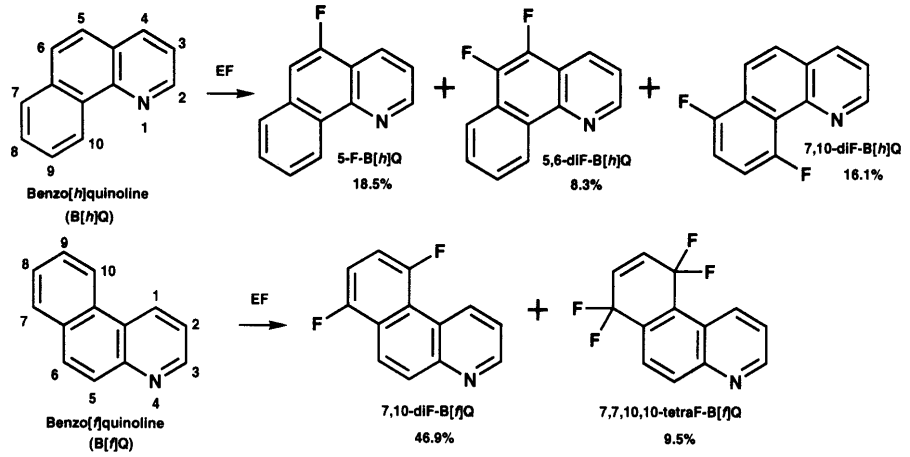


Chart 1. Syntheses of Fluorobenzoquinolines by Electrofluorination

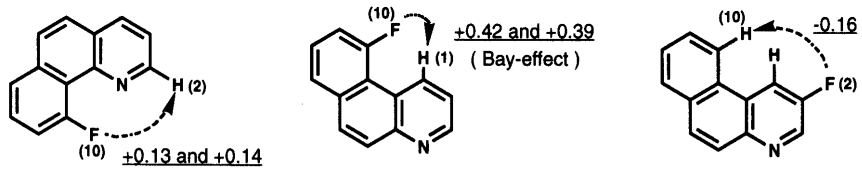


Chart 2. Substituent Effect of F Atom on $^1$H-NMR Chemical Shifts of Aromatic Ring Protons

in 10% yield (Chart 1).

## Discussion

**Electrochemical Fluorination** Using electrochemical partial fluorination, we were successful in synthesizing some fluorinated derivatives in fairly good yields. As expected, fluorination on the pyridine moiety did not occur because of its electron-deficient nature. It is noteworthy that fluorination took place in the K-region of B[*h*]Q but not in that of B[*f*]Q, although the K-region of the latter should also be highly susceptible to an electrophilic reagent. Another noteworthy feature is that at the voltage employed in the present study, B[*f*]Q underwent difluorination at the same carbon to afford the 7,7,10,10-tetrafluorinated product, whereas B[*h*]Q did not. The electrochemical method for achieving partial fluorination, which to date has rarely been applied to *N*-containing aromatic compounds, seems to be a promising tool for synthesis of their fluorinated derivatives.

**Substituent Effect of Fluorine (F) Atom on Basicity of the Ring Nitrogen** As previously reported,[10] fluorine substitution lowers the p$K_a$ values according to the number of chemical bonds between the ring N and substituent F atoms, probably because of the electron-withdrawing inductive effect of the F atom. When a F atom is in spatial proximity to the ring N, the p$K_a$ increases to a remarkable extent. Since fluorine and oxygen atoms are isoelectronic, the former may serve as a hydrogen-acceptor in H-bond formation with $N^+$-H hydrogen, so that the protonated form is more stabilized.

**Substituent Effect of F Atom on $^1$H-NMR Chemical Shifts of Aromatic Ring Protons** The substituent effect of an F atom on the chemical shift of neighboring protons was characterized. The effects were evaluated as follows: ("+" indicates a down-field shift, whereas "−" indicates an up-field shift. S.D.'s are preceded by a ±sign.)

effect on H's at the *ortho*-position
$-0.35 \pm 0.05$ (sample number = 11)
effect on H's at the *para*-position
$-0.21 \pm 0.03$ (sample number = 4)
effect on H's at the *peri*-position
$+0.27 \pm 0.02$ (sample number = 8)

Other types of effects are indicated in Chart 2.

One inconsistency noted was that values obtained by substituting an F atom at the β-position on the α-H of the pyridine ring (3F→2H in B[*h*]Q and 2F→3H in B[*f*]Q) were −0.14 and −0.12, respectively, which are smaller than the expected values. These two values have been excluded from the calculation of the substituent effect at the *ortho*-position described above. It is worth mentioning that spin–spin interaction of nuclei at these positions is also much smaller, even nullified in some cases, than would be expected for *ortho*-positional nuclei.[11]

The fluorinated derivatives of B[*h*]Q and B[*f*]Q synthesized in the present study will be subjected to mutation assays to determine the effect on mutagenicity of varying the site of fluorine substitution.

## Experimental

All starting materials and reagents were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo). Melting points were determined with a Yamato MP-500D micro melting point apparatus without correction. Mass spectra were measured with a JEOL AX 505HA spectrometer. UV spectra were recorded on a Shimadzu UV-2100 spectrophotometer. $^1$H-NMR spectra were measured with a JEOL JMN-EX 270 or a JMN-GSX 400 spectrometer in $CDCl_3$ or DMSO-$d_6$ using tetramethylsilane as an internal standard. The physical constants and $^1$H-NMR data of the fluorinated derivatives synthesized in this study are summarized in Tables 1 and 2. The substituent effect of the fluorine atom on the p$K_a$ of these groups of compounds has been discussed.[8]

**7-Fluorobenzo[*h*]quinoline (7-F-B[*h*]Q)** Benzo[*h*]quinoline was nitrated with 61% nitric acid and concentrated sulfuric acid. The crude product was roughly separated by column chromatography (silica gel, $CHCl_3$). Crude 7-nitro-B[*h*]Q was hydrogenated with 5% Pd–C in

Table 1. Fluorinated Derivatives Synthesized by Methods I to III and Some Physical Constants

| Compound | Synthetic method[a] | mp (°C) | p$K_a$ | $\lambda_{max}$ (nm)[b] | |
|---|---|---|---|---|---|
| | | | | Salt form | Free form |
| Benzo[*h*]quinoline (B[*h*]Q) | | 49—51 | 4.3 | 277, 222 | 266, 232 |
| 3-F-B[*h*]Q | I | 109—110 | 2.0 | 283, 225 | 269, 231 |
| 5-F-B[*h*]Q | III | 80—82 | 3.2 | 281, 224 | 266, 230 |
| 6-F-B[*h*]Q | II | 76—77 | 3.6 | 274, 222 | 263, 229 |
| 7-F-B[*h*]Q | I | 83—85 | 3.5 | 277, 231 | 232 |
| 9-F-B[*h*]Q | I | 85—87 | 3.7 | 280, 221 | 266, 228 |
| 10-F-B[*h*]Q | I | 64—65 | 4.9 | 275, 231 | 232 |
| 3,6-diF-B[*h*]Q | II | 131—132 | 1.5 | 280, 225 | 267, 231 |
| 5,6-diF-B[*h*]Q | III | 143—146 | 2.3 | 279, 225 | 266, 232 |
| 7,10-diF-B[*h*]Q | III | 140—141 | 4.2 | 275, 233 | 232 |
| Benzo[*f*]quinoline (B[*f*]Q) | | 92—93 | 4.7 | 277, 226 | 267, 233 |
| 2-F-B[*f*]Q | I | 109—110 | 2.5 | 281, 225 | 269, 233 |
| 7-F-B[*f*]Q | I | 126—128 | 4.5 | 274, 228 | 233 |
| 10-F-B[*f*]Q | I | 53—56 | 4.3 | 271, 234 | 232 |
| 7,10-diF-B[*f*]Q | III | 125—126 | 4.3 | 267, 230 | 232 |

*a*) I: by Schiemann reaction. II: by Skraup reaction. III: by electrolytic fluorination. *b*) UV spectra of the salt forms were measured in aqueous 1 N HCl (pH 0) and those of the free forms were measured at pH 10 adjusted with aqueous NaOH at room temperature.

Table 2. $^1$H-NMR Chemical Shifts ($\delta$ ppm) of Fluorinated B[*h*]Q's and B[*f*]Q's Measured in $CDCl_3$[a]

| Compound | 1-H | 2-H | 3-F | 4-H | 5-H | 6-H | 7-H | 8-H | 9-H | 10-H |
|---|---|---|---|---|---|---|---|---|---|---|
| B[*h*]Q | / | 9.01 | 7.53 | 8.18 | 7.68 | 7.82 | 7.91 | 7.70 | 7.75 | 9.30 |
| 3-F-B[*h*]Q | / | 8.87 | / | 7.81 | 7.64 | 7.85 | 7.91 | 7.69 | 7.75 | 9.22 |
| 5-F-B[*h*]Q | / | 9.06 | 7.60 | 8.48 | / | 7.46 | 7.85 | 7.68 | 7.71 | 9.24 |
| 6-F-B[*h*]Q | / | 8.97 | 7.54 | 8.14 | 7.33 | / | 8.19 | 7.78 | 7.83 | 9.32 |
| 7-F-B[*h*]Q | / | 9.01 | 7.57 | 8.21 | 7.75 | 8.10 | / | 7.39 | 7.67 | 9.07 |
| 9-F-B[*h*]Q | / | 8.99 | 7.55 | 8.19 | 7.65 | 7.80 | 7.90 | 7.44 | / | 8.92 |
| 10-F-B[*h*]Q | / | 9.14 | 7.56 | 8.21 | 7.71 | 7.82 | 7.74 | 7.64 | 7.46 | / |
| 3,6-diF-B[*h*]Q | / | 8.82 | / | 7.78 | 7.30 | / | 8.18 | 7.82 | 7.78 | 9.20 |
| 5,6-diF-B[*h*]Q | / | 9.02 | 7.62 | 8.47 | / | / | 8.18 | 7.76 | 7.80 | 9.26 |
| 7,10-diF-B[*h*]Q | / | 9.15 | 7.60 | 8.23 | 7.79 | 8.08 | / | 7.29—7.44 | | / |
| B[*f*]Q | 8.96 | 7.57 | 8.96 | / | 8.00 | 8.00 | 9.95 | 7.66 | 7.71 | 8.64 |
| 2-F-B[*f*]Q | 8.53 | / | 8.84 | / | 7.98 | 7.92 | 7.94 | 7.66 | 7.69 | 8.48 |
| 7-F-B[*f*]Q | 8.97 | 7.61 | 9.00 | / | 8.06 | 8.29 | / | 7.35 | 7.64 | 8.41 |
| 10-F-B[*f*]Q | 9.38 | 7.59 | 8.97 | / | 8.04 | 7.98 | 7.76 | 7.60 | 7.41 | / |
| 7,10-diF-B[*f*]Q | 9.35 | 7.60 | 9.00 | / | 8.08 | 8.24 | / | 7.24—7.38 | | / |

*a*) NMR spectra were measured with JNM-EX 270 or JMN-GSX 400 (JEOL), operating at 270 or 400 MHz.

MeOH. Recrystallization from benzene yielded 7-amino-B[*h*]Q as brown plates in 14% yield. mp 175—177 °C.[12] $^1$H-NMR ($CDCl_3$) $\delta$: 4.22 (br s, $D_2O$ exchangeable, $-NH_2$), 7.03 (dd, H-8), 7.51 (d, H-3), 7.55 (t, H-9), 7.66 (d, H-5), 7.85 (dd, H-6), 8.16 (dd, H-4), 8.78 (td, H-10), 8.99 (dd, H-2); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=7.9$, $J_{5-6}=9.2$, $J_{8-9}=7.6$, $J_{8-10}=1.0$, $J_{6-10}=0.7$ Hz.

Isoamyl nitrite (0.87 ml, 3 eq) and 42% $HBF_4$ (1.3 g, 3 eq) were added to 7-amino-B[*h*]Q (400 mg) in MeOH (100 ml) at 0 °C under stirring. After 4 h, the precipitates produced by addition of ether were suspended in xylene (35 ml) and refluxed for 5 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Recrystallization of the residue from benzene-hexane yielded 7-fluoro-B[*h*]Q as colorless needles in 16% yield. mp 83—85 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.39 (ddd, H-8), 7.57 (q, H-3), 7.67 (td, H-9), 7.75 (d, H-5), 8.10 (d, H-6), 8.21 (dd, H-4), 9.01 (dd, H-2), 9.07 (dd, H-10); coupling constants: $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=7.9$, $J_{5-6}=9.2$, $J_{9-10}=8.3$, $J_{8-10}=1.0$, $J_{F-8}=10.2$, $J_{F-9}=5.6$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 78.88; H, 4.40; N, 6.83.

**9-Fluorobenzo[*h*]quinoline (9-F-B[*h*]Q)** Benzo[*h*]quinoline (2 g) was nitrated with 61% nitric acid and concentrated sulfuric acid. Crude 9-nitro-B[*h*]Q was recrystallized from benzene twice. mp 237—239 °C.[12] $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.83 (dd, H-3), 8.14 (d, H-5 or H-6), 8.17 (d, H-5 or H-6), 8.32 (d, H-7), 8.51 (dd, H-8), 8.56 (dd, H-4), 9.13 (dd, H-2), 9.96 (d, H-10); coupling constants, $J_{2-3}=4.4$, $J_{2-4}=1.8$, $J_{3-4}=8.1$, $J_{5-6}=8.9$, $J_{7-8}=8.8$, $J_{8-10}=2.4$ Hz.

9-Nitro-B[*h*]Q (293 mg) was hydrogenated with 5% Pd–C in MeOH containing HCl. Without any purification, the 9-amino-B[*h*]Q thus produced was dissolved in MeOH (100 ml) and the solution was mixed at 0 °C with 42% $HBF_4$ (996 mg, 3.6 eq) and isoamyl nitrite (0.35 ml, 2 eq). After 4 h, the precipitates produced by addition of ether were washed with ether and hexane, and then suspended in xylene and refluxed (30 ml) for 9 h. The reaction mixture was extracted with 10% HCl. The aqueous layer was neutralized and extracted with ether. Purification of the extract by column chromatography (silica gel, $CHCl_3$) afforded 9-fluoro-B[*h*]Q in 17% yield from 9-$NO_2$-B[*h*]Q. mp 85—87 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.44 (m, H-8), 7.55 (dd, H-3), 7.65 (d, H-5), 7.80 (d, H-6), 7.90 (dd, H-7), 8.19 (dd, H-4), 8.92 (dd, H-10), 8.99 (dd, H-2); coupling constants, $J_{2-3}=4.4$, $J_{2-4}=1.7$, $J_{5-6}=8.9$, $J_{7-8}=8.7$, $J_{8-10}=2.8$, $J_{7-F}=5.6$, $J_{8-F}=8.2$, $J_{F-10}=10.7$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.53; H, 4.18; N, 7.28.

**10-Fluorobenzo[*h*]quinoline (10-F-B[*h*]Q)** Benzo[*h*]quinoline was nitrated with 61% nitric acid and concentrated sulfuric acid. The crude product was separated by column chromatography (silica gel, $CHCl_3$). 10-Nitro-B[*h*]Q was obtained as a colorless solid in 8% yield. mp 168—169 °C.[12] MS *m/z*: 224 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.57 (q, H-3), 7.69 (dd, H-7), 7.73 (t, H-8), 7.81 (d, H-5), 7.87 (d, H-6), 8.06 (dd, H-9), 8.21 (dd, H-4), 8.94 (dd, H-2); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=8.3$, $J_{5-6}=8.9$, $J_{7-8}=7.6$, $J_{7-9}=2.0$, $J_{8-9}=7.6$ Hz.

10-Nitro-B[*h*]Q was hydrogenated with 5% Pd–C in MeOH. Purification by column chromatography (aluminium oxide, benzene) gave 10-amino-B[*h*]Q as a yellow solid in 39% yield. mp 93—94 °C.[12] MS

*m/z*: 194 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 1.65 (br s, $D_2O$ exchangeable, $-NH_2$), 6.95 (dd, H-9), 7.22 (dd, H-7), 7.45 (q, H-3), 7.47 (t, H-8), 7.57 (d, H-5), 7.72 (d, H-6), 8.15 (dd, H-4), 9.11 (dd, H-2); coupling constants, $J_{2-3}=4.6$, $J_{2-4}=2.0$, $J_{3-4}=7.9$, $J_{5-6}=8.9$, $J_{7-8}=7.9$, $J_{7-9}=1.0$, $J_{8-9}=7.6$ Hz.

Isoamyl nitrite (0.32 ml, 3 eq) and 42% $HBF_4$ (472 mg, 3 eq) were added to 10-amino-B[*h*]Q (149 mg) in MeOH (15 ml) at 0 °C under stirring. After 4 h, the precipitates produced by addition of ether were suspended in xylene (50 ml) and refluxed for 2 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. 10-Fluoro-B[*h*]Q was obtained as a colorless solid in 0.8% yield. mp 64—65 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.46 (ddd, H-9), 7.56 (q, H-3), 7.64 (td, H-8), 7.71 (d, H-5), 7.74 (dd, H-7), 7.82 (dd, H-6), 8.21 (dd, H-4), 9.14 (m, H-2); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=8.3$, $J_{5-6}=8.9$, $J_{7-8}=7.9$, $J_{7-9}=1.3$, $J_{8-9}=7.9$, $J_{F-2}=2.0$, $J_{F-6}=2.0$, $J_{F-8}=4.6$, $J_{F-9}=13.2$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.10; H, 4.17; N, 7.10.

**7-Fluorobenzo[*f*]quinoline (7-F-B[*f*]Q)** Benzo[*f*]quinoline was nitrated with 61% nitric acid and concentrated sulfuric acid. Crude 7-nitro-B[*f*]Q was recrystallized twice from benzene to afford yellow needles. mp 162—164 °C.[12] MS *m/z*: 224 ($M^+$), 178 ($M^+-NO_2$), 166 ($M^+-CNO_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.67 (q, H-2), 7.80 (t, H-9), 8.23 (d, H-5), 8.23 (dd, H-8), 8.59 (dd, H-6), 8.93 (dd, H-10), 8.99 (dd, H-1), 9.07 (dd, H-3); coupling constants, $J_{1-2}=8.6$, $J_{1-3}=1.3$, $J_{2-3}=4.3$, $J_{5-6}=9.6$, $J_{8-9}=7.6$, $J_{8-10}=1.3$, $J_{9-10}=8.6$, $J_{6-10}=0.7$ Hz.

7-Nitro-B[*f*]Q was hydrogenated with 5% Pd–C in MeOH. Recrystallization from benzene yielded 7-amino-B[*f*]Q as brown plates. mp 175—177 °C.[12] MS *m/z*: 194 ($M^+$), 166 ($M^+-CNH_2$). $^1$H-NMR ($CDCl_3$) $\delta$: 4.26 (br s, $D_2O$ exchangeable, $-NH_2$), 6.98 (d, H-8), 7.47—7.56 (m, H-2 and H-9), 7.96 (d, H-5), 8.03 (d, H-6), 8.09 (d, H-10), 8.93—8.96 (m, H-1 and H-3); coupling constants, $J_{5-6}=9.2$, $J_{8-9}=7.6$, $J_{9-10}=8.3$ Hz.

7-Amino-B[*h*]Q (1.09 g) in MeOH (200 ml) was mixed at 0 °C with 42% $HBF_4$ (3.51 g, 3 eq) and isoamyl nitrite (2.36 ml, 3 eq). After 4 h, the precipitates produced by addition of ether were suspended in xylene (35 ml) and refluxed for 5 h. The reaction mixture was filtered and the filtrate was purified by column chromatography (aluminium oxide, benzene). Recrystallization from benzene–hexane yielded 7-fluoro-B[*h*]Q as colorless needles in 22% yield. mp 126—128 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.35 (ddd, H-8), 7.61 (q, H-2), 7.64 (td, H-9), 8.06 (d, H-5), 8.29 (d, H-6), 8.41 (dd, H-10), 8.97 (dd, H-1), 9.00 (dd, H-3); coupling constants, $J_{1-2}=8.6$, $J_{1-3}=1.7$, $J_{2-3}=4.6$, $J_{5-6}=9.2$, $J_{8-9}=7.9$, $J_{8-10}=1.0$, $J_{9-10}=8.3$, $J_{F-8}=10.2$, $J_{F-9}=5.6$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.12; H, 4.33; N, 6.91.

**10-Fluorobenzo[*f*]quinoline (10-F-B[*f*]Q)** Benzo[*f*]quinoline was nitrated with 61% nitric acid and concentrated sulfuric acid. Crude 10-nitro-B[*f*]Q was hydrogenated with 5% Pd–C in MeOH. The crude product was isolated as a pale brown solid by column chromatography (silica gel, $CHCl_3$ : MeOH = 19 : 1). mp 153—157 °C.[12] $^1$H-NMR ($CDCl_3$) $\delta$: 4.33 (s, $D_2O$ exchangeable, $-NH_2$), 7.06 (dd, H-9), 7.43—7.47 (m, H-7 and H-8), 7.50 (q, H-2), 7.91 (s, H-5 and H-6), 8.89 (dd, H-3), 9.64 (dd, H-1); coupling constants, $J_{1-2}=8.6$, $J_{1-3}=1.7$, $J_{2-3}=4.3$ Hz.

10-Amino-B[*f*]Q (119 mg) in MeOH (15 ml) was mixed at 0 °C with 42% $HBF_4$ (365 mg, 3 eq) and isoamyl nitrite (0.25 ml, 3 eq). After 4 h, the precipitates produced by addition of ether were suspended in xylene (60 ml) and refluxed for 2 h. The reaction mixture was filtered and the filtrate was purified by column chromatography (silica gel, $CHCl_3$ : MeOH = 19 : 1). 10-Fluoro-B[*f*]Q was obtained as a pale yellow solid in 21% yield. mp 53—56 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.41 (ddd, H-9), 7.59 (q, H-2), 7.60 (m, H-8), 7.76 (dd, H-7), 7.98 (dd, H-6), 8.04 (d, H-5), 8.97 (d, H-3), 9.38 (m, H-1); coupling constants, $J_{1-2}=8.3$, $J_{2-3}=4.6$, $J_{1-3}=1.7$, $J_{5-6}=9.2$, $J_{7-8}=7.9$, $J_{7-9}=1.3$, $J_{F-1}=3.0$, $J_{F-6}=2.0$, $J_{F-8}=5.0$, $J_{F-9}=13.9$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 78.88; H, 4.40; N, 6.83.

**3-Fluorobenzo[*h*]quinoline (3-F-B[*h*]Q)** 3-Amino-B[*h*]Q[7] (263 mg) in MeOH (20 ml) was mixed at 0 °C with 42% $HBF_4$ (836 mg, 3 eq) and isoamyl nitrite (0.56 ml, 3 eq). After 4 h, the precipitates produced by addition of ether were suspended in xylene (20 ml) and refluxed for 2 h. The reaction mixture was filtered and the filtrate was purified by column chromatography (silica gel, $CHCl_3$ : hexane = 8 : 2). Recrystallization from benzene–hexane yielded 3-fluoro-B[*h*]Q as colorless needles in 57% yield. mp 109—110 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.64 (d, H-5), 7.69 (td, H-8), 7.75 (td, H-9), 7.81 (dd, H-4), 7.85 (d, H-6), 7.91 (m, H-7), 8.87 (d, H-2), 9.22 (m, H-10); coupling constants, $J_{F-2}=\sim 0$, $J_{2-4}=3.0$, $J_{F-4}=8.9$, $J_{5-6}=8.6$, $J_{7-8}=7.6$, $J_{8-9}=7.3$, $J_{7-9}=1.7$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.41; H, 4.43; N, 7.06.

**2-Fluorobenzo[*f*]quinoline (2-F-B[*f*]Q)** 2-Amino-B[*f*]Q[7] (192 mg) in MeOH (15 ml) was mixed at 0 °C with 42% $HBF_4$ (609 mg, 3 eq) and isoamyl nitrite (0.41 ml, 3 eq). After 4 h, the precipitates produced by addition of ether were suspended in xylene (15 ml) and refluxed for 2 h. The reaction mixture was filtered and the filtrate was purified by column chromatography (silica gel, $CHCl_3$). 2-Fluoro-B[*f*]Q was obtained as pale brown solid in 49% yield. mp 109—110 °C. $^1$H-NMR ($CDCl_3$) $\delta$: 7.66 (m, H-8), 7.69 (m, H-9), 7.92 (d, H-6), 7.94 (m, H-7), 7.98 (dd, H-5), 8.48 (m, H-10), 8.53 (dd, H-1), 8.84 (d, H-3); coupling constants, $J_{F-1}=9.9$, $J_{F-3}=ca.\ 0$, $J_{1-3}=2.6$, $J_{1-5}=0.7$, $J_{5-6}=9.2$, $J_{7-8}=6.3$, $J_{8-9}=6.9$, $J_{7-9}=3.0$, $J_{8-10}=2.6$, $J_{9-10}=5.8$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.04; H, 4.29; N, 6.91.

**6-Fluorobenzo[*h*]quinoline (6-F-B[*h*]Q)** 1-Amino-4-fluoronaphthalene[13] (583 mg), glycerol (828 mg, 2.5 eq) and sodium *m*-nitrobenzenesulfonate (2 g, 2.5 eq) were dissolved in 80% $H_2SO_4$ (20 ml) and the mixture was stirred at 140 °C for 4 h. The reaction mixture was poured into ice water (100 ml). The filtrate was neutralized with NaOH solution and extracted with $CHCl_3$ (200 ml × 2). Purification of the extract by column chromatography (aluminium oxide, benzene : hexane = 8 : 2) gave 6-fluoro-B[*h*]Q in 15% yield. mp, 76—77 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.33 (d, H-5), 7.54 (q, H-3), 7.78 (td, H-8), 7.83 (td, H-9), 8.14 (dd, H-4), 8.19 (dd, H-7), 8.97 (dd, H-2), 9.32 (m, H-10); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.3$, $J_{3-4}=7.9$, $J_{F-5}=10.9$, $J_{7-8}=7.3$, $J_{7-9}=2.3$, $J_{8-9}=6.9$, $J_{8-10}=1.7$, $J_{9-10}=6.9$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.18; H, 4.09; N, 7.10. Found: C, 79.09; H, 4.31; N, 6.96.

**3,6-Difluorobenzo[*h*]quinoline (3,6-diF-B[*h*]Q)** 1-Amino-4-fluoronaphthalene (839 mg) was treated with sodium nitromalonaldehyde monohydrate[7] (817 mg, 1 eq) in 2% aqueous HCl (40 ml) at 50 °C for 30 min to give *N*-(2-formyl-2-nitroethylidene)-4-fluoro-1-naphthylamine, which was then treated with $ZnCl_2$ in dimethylacetamide at 180 °C for 2.5 h. Purification by column chromatography (aluminium oxide, $CHCl_3$ : hexane = 8 : 2) gave 6-fluoro-3-nitro-B[*h*]Q in 29% yield. $^1$H-NMR ($CDCl_3$) $\delta$: 7.43 (d, H-5), 7.87—7.92 (m, H-8 and H-9), 8.25 (m, H-7), 8.92 (d, H-4), 9.30 (d, H-10), 9.66 (d, H-2); coupling constants, $J_{2-4}=2.7$, $J_{5-F}=10.3$ Hz.

6-Fluoro-3-nitro-B[*h*]Q (570 mg) was catalytically hydrogenated quantitatively with 5% Pd–C in EtOH to 3-amino-6-F-B[*h*]Q. $^1$H-NMR ($CDCl_3$) $\delta$: 3.98 (br s, $D_2O$ exchangeable, $-NH_2$), 7.15 (d, H-5), 7.25 (d, H-4), 7.64 (ddd, H-9), 7.73 (ddd, H-8), 8.10 (d, H-7), 8.48 (d, H-2), 9.09 (dd, H-10); coupling constants, $J_{2-4}=3.0$, $J_{5-F}=11.0$, $J_{7-8}=7.9$, $J_{7-9}=1.2$, $J_{8-9}=7.3$, $J_{8-10}=1.2$, $J_{8-10}=8.5$, $J_{F-10}=1.2$ Hz.

3-Amino-6-F-B[*h*]Q (451 mg) in EtOH (50 ml) was mixed at 0 °C with 42% $HBF_4$ (1.7 ml, 5 eq) and isoamyl nitrite (0.89 ml, 3 eq). The precipitates produced by addition of ether were suspended in xylene (100 ml) and refluxed for 1 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. Recrystallization from EtOH yielded 3,6-difluoro-B[*h*]Q as a colorless solid in 49% yield. mp 131—132 °C. MS *m/z*: 215 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.30 (d, H-5), 7.78 (dd, H-4), 7.78 (ddd, H-9), 7.82 (ddd, H-8), 8.18 (dd, H-7), 8.82 (d, H-2), 9.20 (ddd, H-10); coupling constants, $J_{2-3F}=ca.\ 0$, $J_{2-4}=2.7$, $J_{3F-4}=8.9$, $J_{5-6F}=10.8$, $J_{7-8}=7.9$, $J_{7-9}=1.3$, $J_{8-9}=7.6$, $J_{8-10}=1.3$, $J_{9-10}=8.2$, $J_{6F-10}=1.7$ Hz. *Anal.* Calcd for $C_{13}H_7F_2N$: C, 72.56; H, 3.28; N, 6.51. Found: C, 72.61; H, 3.59; N, 6.28.

**Electrochemical Fluorination of Benzo[*h*]quinoline** Preparation of the electrolyte, $Bu_4N\cdot 4.45HF$, was carried out without solvent, and electrolysis was performed as reported by Momota *et al.*[9] B[*h*]Q (40.4 mmol) dissolved in 250 ml of $Bu_4N\cdot 4.45HF$ was subjected to electrolysis at a platinum anode at a constant voltage of 2.5 V. The electrolysis was allowed to continue for 12.5 h, until the quantity of electricity consumed amounted to 14960 coulombs. The reaction mixture was poured into chilled water, neutralized with 48% KOH, and extracted with $CH_2Cl_2$. The extract was evaporated *in vacuo* to give 8.7 g of a solid. Purification by column chromatography (silica gel, $CH_2Cl_2$ : hexane = 1 : 1 → $CH_2Cl_2$ → $CH_2Cl_2$ : ether = 4 : 1) gave the following three products.

**5,6-Difluoro-B[*h*]Q** Colorless needles in 8.3% yield. mp 143—146 °C. MS *m/z*: 215 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.62 (q, H-3), 7.76 (td, H-8), 7.80 (td, H-9), 8.18 (m, H-7), 8.47 (dd, H-4), 9.02 (dd, H-2), 9.26 (m, H-10); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=8.3$,

$J_{7-8}=7.4$, $J_{7-9}=2.6$, $J_{8-9}=7.3$ Hz. *Anal.* Calcd for $C_{13}H_7F_2N$: C, 72.55; H, 3.29; N, 6.51. Found: C, 72.79; H, 3.46; N, 6.69.

**5-Fluoro-B[*h*]Q** Colorless needles in 18.5% yield. mp 80—82 °C. MS *m/z*: 197 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.46 (d, H-6), 7.60 (q, H-3), 7.68 (td, H-8), 7.71 (td, H-9), 7.85 (m, H-7), 8.48 (dd, H-4), 9.06 (dd, H-2), 9.24 (m, H-10); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=8.3$, $J_{F-6}=10.9$ Hz. *Anal.* Calcd for $C_{13}H_8FN$: C, 79.17; H, 4.10; N, 7.10. Found: C, 79.36; H, 4.39; N, 7.48.

**7,10-Difluoro-B[*h*]Q** Colorless needles in 16.1% yield. mp 140—141 °C. MS *m/z*: 215 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.29—7.44 (m, H-8 and H-9), 7.60 (q, H-3), 7.79 (d, H-5), 8.08 (dd, H-6), 8.23 (dd, H-4), 9.15 (dd, H-2); coupling constants, $J_{2-3}=4.3$, $J_{2-4}=1.7$, $J_{3-4}=8.1$, $J_{5-6}=9.2$, $J_{10F-6}=2.0$, $J_{10F-2}=1.3$ Hz. *Anal.* Calcd for $C_{13}H_7F_2N$: C, 72.55; H, 3.29; N, 6.51. Found: C, 72.30; H, 3.60; N, 6.19.

**Electrochemical Fluorination of Benzo[*f*]quinoline** Electrolysis was carried out as reported by Momota *et al.*[9] B[*f*]Q (40.4 mmol) dissolved in 250 ml of $Bu_4N\cdot 4.45HF$ was subjected to electrolysis at a platinum anode at a constant voltage of 2.7 V. The electrolysis was allowed to continue for 9 h, until the quantity of electricity consumed amounted to 14960 coulombs. The reaction mixture was poured into chilled water, neutralized with 48% KOH, and extracted with $CH_2Cl_2$. The extract was evaporated *in vacuo* to give 8.2 g of a solid. Purification by column chromatography (silica gel, $CH_2Cl_2\rightarrow CH_2Cl_2$ : ether = 4 : 1) gave the following two products.

**7,7,10,10-Tetrafluoro-B[*f*]Q** Colorless needles in 9.5% yield. mp 103—106 °C. MS *m/z*: 253 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 6.53—6.60 (m, H-8 and H-9), 7.59 (q, H-2), 8.04 (d, H-5), 8.36 (d, H-6), 8.86 (dd, H-1), 9.06 (dd, H-3); coupling constants, $J_{1-2}=8.9$, $J_{2-3}=4.3$, $J_{1-3}=1.6$, $J_{5-6}=8.9$ Hz. *Anal.* Calcd for $C_{13}H_7F_4N$: C, 61.66; H, 2.79; N, 5.53. Found: C, 63.57; H, 3.13; N, 5.70.

**7,10-Difluoro-B[*f*]Q** Colorless needles in 46.9% yield. mp 125—126 °C. MS *m/z*: 215 ($M^+$). $^1$H-NMR ($CDCl_3$) $\delta$: 7.24—7.38 (m, H-8 and H-9), 7.60 (q, H-2), 8.08 (d, H-5), 8.24 (dd, H-6), 9.00 (dd, H-3), 9.35 (m, H-1); coupling constants, $J_{1-2}=8.6$, $J_{2-3}=4.3$, $J_{1-3}=1.7$, $J_{5-6}=9.2$, $J_{10F-1}=3.6$, $J_{10F-2}=1.3$, $J_{10F-6}=2.0$ Hz. *Anal.* Calcd for $C_{13}H_7F_2N$: C, 72.55; H, 3.29; N, 6.51. Found: C, 72.71; H, 3.58; N, 6.71.

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**References**

1) Jerina D. M., Yagi H., Lehr R. E., Thakker D. R., Schaefer-Ridder M., Karle J. M., Levin W., Wood A. W., Chang R. L., Conney A. H., "Polycyclic Hydrocarbons Cancer," Vol. 1, ed. by Gelboin H. V., Ts'o Paul O. P., Academic Press, New York, 1978, pp. 173—188.
2) McCann J., Choi E., Yamazaki E., Ames B. N., *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 5135—5139 (1975); Hirano K., Shinohara Y., Tsuda H., Fukushima S., Takahashi M., Ito N., *Cancer Res.*, **36**, 329—335 (1976).
3) Tada M., Takahashi K., Kawazoe Y., *Chem. Pharm. Bull.*, **30**, 3834—3837 (1982); *idem*, *Chem.-Biol. Interactions*, **29**, 257—266 (1980); Saeki K., Takahashi K., Kawazoe Y., *Biol. Pharm. Bull.*, **19**, 541—546 (1996).
4) Takahashi K., Kamiya M., Sengoku Y., Kohda K., Kawazoe Y., *Chem. Pharm. Bull.*, **36**, 4630—4633 (1988); Kamiya M., Sengoku Y., Takahashi K., Kohda K., Kawazoe Y., "Antimutagenesis and Anticarcinogenesis," II, ed. by Kuroda Y., Shankel D. M., Waters M. D., Plenum Publishing Corp., New York, 1990, pp. 441—446; Saeki K., Takahashi K., Kawazoe Y., *Biol. Pharm. Bull.*, **16**, 232—234 (1993).
5) LaVoie E. J., Tulley-Freiler L., Bedenko V., Hoffmann D., *Mutation Res.*, **116**, 91—102 (1983); Hecht S. S., LaVoie E. J., Bedenko V., Pingaro L., Katayama S., Hoffmann D., Sardella D. J., Boger E., Lehr R. E., *Cancer Res.*, **41**, 4341—4345 (1981); Hubenman E., Slaga T. J., *ibid.*, **39**, 411—414 (1979); Diamond L., Cherian K., Harvey R. G., DiGiovanni J., *Mutation Res.*, **136**, 65—72 (1984); Miller E. C., Miller J. A., *Cancer Res.*, **20**, 133—137 (1960); Miller J. A., Miller E. C., Finger G. C., *ibid.*, **13**, 93—97 (1953); *idem.*, *ibid.*, **17**, 387—398 (1957).
6) For example; Welch J. T., *Tetrahedron*, **43**, 3123—3197 (1987).
7) Takeuchi I., Hamada Y., Hirota M., *Chem. Pharm. Bull.*, **41**, 747—751 (1993).
8) Momota K., Morita M., Matsuda Y., *Electrochimica Acta*, **38**, 619—624 (1993); *idem*, *ibid.*, **38**, 1123—1130 (1993); Momota K., Kato K., Morita M., Matsuda Y., *ibid.*, **39**, 41—47 (1994); Morita K., Kato K., Morita M., Matsuda Y., *ibid.*, **39**, 681—690 (1994); Momota K., Horio H., Kato K., Morita M., Matsuda Y., *ibid.*, **40**, 233—240 (1995); and references cited therein.
9) Momota K., Yonezawa T., Hayakawa Y., Kato K., Morita M., Matsuda Y., *J. Applied Electrochem.*, **25**, 651—658 (1995).
10) Wei W., Saeki K., Kawazoe Y., *Heterocycles*, **41**, 315—322 (1995).
11) Saeki K., Kohda K., Kawazoe Y., Sakamoto Y., *Heterocycles*, **33**, 35—38 (1992).
12) Iwai K., Hara S., *Yakugaku Zasshi*, **70**, 394—400 (1950); Iwai K., Hara S., Saeki S., *ibid.*, **71**, 1152—1158 (1951); Ochiai E., Tamura S., *ibid.*, **72**, 985—988 (1952).
13) Adcock W., Dewar J. S., *J. Am. Chem. Soc.*, **89**, 386—390 (1967).