The Synthesis of Benzofuroquinolines. VI. A New Synthesis of Benzofuro[2,3-*c*]quinoline Derivatives

Seiji YAMAGUCHI,* Yutaka OH-HIRA, Minoru YAMADA, Hitomi MICHITANI, and Yoshiyuki KAWASE
Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930
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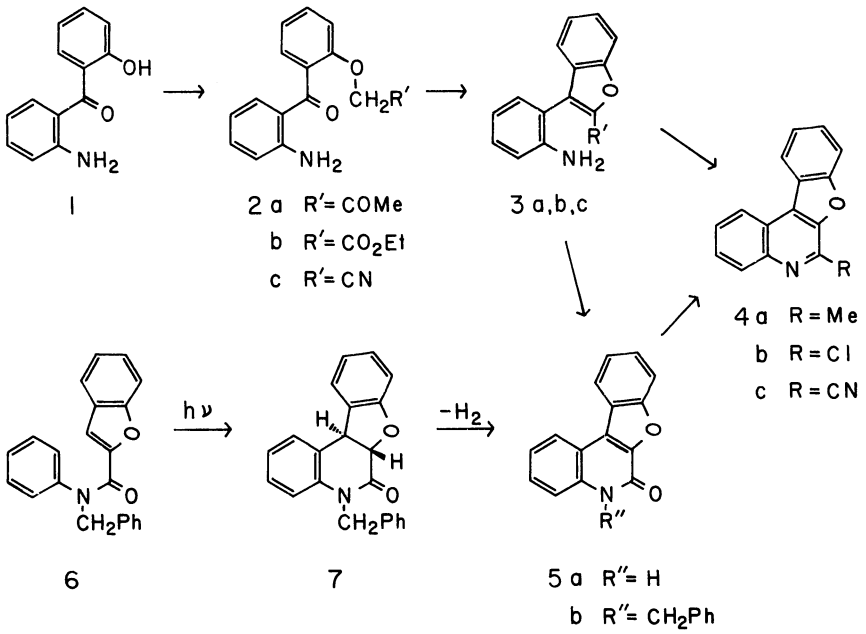
Synopsis. Two benzofuro[2,3-*c*]quinoline derivatives, 6-methylbenzofuro[2,3-*c*]quinoline and 6(5*H*)-benzofuro[2,3-*c*]quinolinone, were synthesized by the condensation of 2-amino-2′-hydroxybenzophenone with chloroacetone, ethyl bromoacetate, or chloroacetonitrile. The benzofuroquinolinone, thus obtained, was converted to 6-chloro and 6-cyanobenzofuro[2,3-*c*]quinolines.

In the course of our studies of polycyclic heteroaromatic compounds, we studied the synthesis of benzofuroquinolines in order to test their activities as mutagens, carcinogens, and also antitumor substances. In our previous papers, we reported the syntheses of some benzofuro[2,3-*b*]-,[1] [3,2-*b*]-,[2] and [3,2-*c*]quinolines.[1] In this paper we report on a new synthesis of benzofuro[2,3-*c*]quinolines. Fryer et al. reported that 10-chloro-5-(2-dimethylaminoethyl)-5,7-dihydro-6*H*-indolo[2,3-*c*]quinolin-6-one having a similar skeleton showed a strong anti-tumor activity.[3] We therefore expect some activities for benzofuro[2,3-*c*]quinolinones.

Two benzofuro[2,3-*c*]quinolinones have already been reported: 5-methylbenzofuro[2,3-*c*]quinolin-6(5*H*)-one (**5**: R″=Me) was prepared by photocyclization of *N*-methyl-*N*-phenyl-2-benzofurancarboxamide[4] and its 2-chloro derivative was prepared by cyclization of 6-chloro-4-(2-fluorophenyl)-3-hydroxy-2(1*H*)-quinolinone.[5] However, these are syntheses only to benzofuro[2,3-*c*]quinolin-6(5*H*)-ones. So, we planed a new approach to various derivatives of benzofuro-[2,3-*c*]quinoline.

Our key intermediate, 2-amino-2′-hydroxybenzophenone (**1**), was prepared by the demethylation of 2-amino-2′-methoxybenzophenone.[6] Condensation of **1** with chloroacetone gave 6-methylbenzofuro[2,3-*c*]quinoline (**4a**) in 56% yield after refluxing with potassium carbonate in acetone. Similar condensations of **1** with chloroacetaldehyde or chloroacetaldehyde dimethyl acetal did not afford unsubstituted benzofuro[2,3-*c*]quinoline (**4**: R=H). A similar condensation of **1** with ethyl bromoacetate gave ethyl 2-(2-aminobenzoyl)phenoxyacetate (**2b**) (52%), which was easily converted to benzofuro[2,3-*c*]quinolin-6(5*H*)-one (**5a**) in 53% by treating the mixture with sodium ethoxide. Similarly, **1** was condensed with chloroacetonitrile to give [2-(2-aminobenzoyl)phenoxy]acetonitrile (**2c**) (94%), which was converted to **5a** in 61% by refluxing with potassium hydroxide in 2-ethoxyethanol for 6 h. A mild treatment of **2c** with potassium hydroxide in refluxing ethanol gave 3-(2-aminophenyl)-2-benzofurancarbonitrile (**3c**) (73%), which was also converted to **5a** in 57% by refluxing with potassium hydroxide in 2-ethoxyethanol.

The structure of **5a** was confirmed by a direct comparison with a sample prepared according to the method reported by Kanaoka and San-nohe.[4] Thus, *N*-benzyl-*N*-phenyl-2-benzofurancarboxamide (**6**) was converted to 5-benzylbenzofuro[2,3-*c*]quinolin-6(5*H*)-one (**5b**) by photocyclization to **7** followed by dehydrogenation of **7**. Debenzylation of **5b** was effective by refluxing with methanesulfonic acid to



give **5a** (40%), which was identical with a sample synthesized from **1**.

Chlorination of **5a** with phosphorus pentachloride in refluxing phosphoryl chloride gave 6-chlorobenzofuro[2,3-*c*]quinoline (**4b**) (86%), which was converted to 6-cyanobenzofuro[2,3-*c*]quinoline (**4c**) in 29% by refluxing with sodium cyanide in DMF. The 6-chloro derivative, **4b**, showed a similar UV spectrum as the 6-methyl derivative, **4a**.

Experimental

All melting points are uncorrected. IR spectra were measured using a Hitachi EPI-S2 spectrophotometer in potassium bromide disks; UV spectra were measured using a Hitachi 220A spectrophotometer in ethanolic solutions. Mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer; ^{1}H NMR spectra were recorded on a JEOL PMX-60Si NMR spectrometer.

2-Amino-2′-hydroxybenzophenone (1). To a suspension of anhydrous aluminum chloride (17.1 g) in dry benzene (550 ml) was added a solution of 2-amino-2′-methoxybenzophenone[6] (13.6 g, 59.9 mmol) in dry benzene (300 ml) for 1.5 h; the mixture was then heated under reflux for 1 h. The hot reaction mixture was poured into dilute hydrochloric acid. After cooling, the mixture was neutralized with 5% sodium hydroxide, and the benzene layer was collected. The aqueous layer was extracted again with ether, and the ether layer was combined with the benzene layer. The combined extracts were re-extracted with a 5% sodium hydroxide solution. The alkaline layer was neuralized to ca. pH 7 with 10% hydrochloric acid and re-extracted with ether. This ether layer was washed with a sat. sodium chloride solution and dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, crude 2-amino-2′-hydroxybenzophenone (**1**) was obtained as a yellow oil in 94% yield: IR (liquid film) 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.9 (2H, s, NH_2), 11.3 (1H, s, OH); MS *m/z* 213 (M^+). This aminophenol **1** showed one spot in TLC and was used for the next step without further purification.[7]

6-Methylbenzofuro[2,3-*c*]quinoline (4a). A solution of **1a** (1.59 g, 7.46 mmol) in dry acetone (50 ml) was treated with anhydrous potassium carbonate (2.1 g, 15 mmol) and potassium iodide (1.3 g, 7.8 mmol); the mixture was then heated under refluxed for 30 m with stirring. To this mixture was added a solution of chloroacetone (720 mg, 7.78 mmol) in dry acetone (10 ml); the mixture was heated under reflux for 4h with stirring. After cooling, the mixture was diluted with cold water. The precipitates were recrystallized from ethanol to give 6-methylbenzofuro[2,3-*c*]quinoline (**4a**) (1.22 g, 70%) as colorless needles: mp 125.5—126.5 °C; UV 238 (log ε 4.65), 243 (4.70), 308 (4.28), 322 nm (4.18); ^{1}H NMR ($CDCl_3$) δ=3.0(3H, s, 6-Me); Found: C, 82.64; H, 4.73; N, 6.13%; M^+, 233. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01%; M, 233.

Benzofuro[2,3-*c*]quinolin-6(5*H*)-one (5a). From 1 and Ethyl Bromoacetate: According to the procedure described above for **4a**, **1** (3.06 g, 14.4 mmol) was treated with ethyl bromoacetate (2.97 g, 17.8 mmol). An yellow oil was obtained as ether extracts and was crystallized from benzene-cyclohexane to give ethyl 2-(2-aminobenzoyl)phenoxyacetate (**2b**) (2.25 g, 52%) as pale yellow plates: mp 81—81.5 °C; IR 1730 (ester CO) and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.3 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 4.2 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH_3$), 4.6 (2H, s, COH_2CO_2Et), 6.0 (2H, s, NH_2); Found: C, 68.32; H, 5.70; N, 4.69%; M^+, 299. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68%; M, 299. This ester **2b** (2.06 g, 6.89 mmol) was dissloved in ethanol (40 ml) and added to a cold ethanolic sodium ethoxide solution, prepared from sodium metal (0.50 g, 21.7 mmol) and ethanol (30 ml); the mixture was stirred at room temperature for 1.5 h, and poured into dilute hydrochloric acid. The precipitates were recrystallized from 2-ethoxyethanol to give benzofuro[2,3-*c*]quinolin-6(5*H*)-one (**5a**) (0.85 g, 53%) as colorless powder: mp 322—324 °C; IR 1675 cm^{-1}; UV 224 (log ε 4.68), 233sh (4.57), 240sh (4.49), 263 (3.90), 275sh (3.90), 285 (4.06), 295 (4.15), 313sh (3.91), 322 (3.99), 337 nm (3.85); Found: C, 76.85; H, 4.01; N, 6.24%; M^+. 235. Calcd for $C_{15}H_9NO_2$: C, 76.58; H, 3.86; N, 5.96; M, 235.

From 1 and Chloroacetonitrile: According to the procedure described above, **1** (4.07 g, 19.1 mmol) was similarly treated with chloroacetonitrile (2.13 g, 28.2 mmol) to give 2-amino-2′-(cyanomethyloxy)benzophenone (**2c**) (4.50 g, 94%) as pale yellow needles after crystallization from benzene–hexane: mp 95—96 °C; IR 1630 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ=4.6 (2H, s, OCH_2CN), 6.3 (2H, s, NH_2); Found: C, 71.38; H, 4.80; N, 11.11%; M^+, 252. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11; M, 252. To a solution of this cyanomethoxy intermediate **2c** (1.17 g, 4.64 mmol) in 2-ethoxyethanol (50 ml), potassium hydroxide (1.30 g, 23.1 mmol) was added; the mixture was heated under reflux under nitrogen atmosphere for 6 h with stirring. After cooling, the mixture was poured into dilute hydrochloric acid. The precipitates were recrystallized from 2-ethoxyethanol to give **5a** (660 mg, 61%). However, a similar treatment of **2c** with potassium hydroxide in refluxing ethanol gave 3-(2-aminophenyl)-2-benzofurancarbonitrile (**3c**) as a colorless powder in 97%: mp 247.5—248 °C; Found: C, 76.99; H, 4.25; N, 11.89%; M^+, 234. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96%; M, 234. This intermediate benzofuran **3c** was converted to **5a** in 57% by an additional treatment with potassium hydroxide in refluxing 2-ethoxyethanol.

Photocyclization: According to a procedure reported by Kanaoka and San-nohe,[4] a solution of *N*-benzyl-*N*-phenyl-2-benzofurancarboxamide (**6**) (2.00 g, 6.12 mmol) in acetonitrile (200 ml) was irradiated under nitrogen atmosphere for 45 h using a 100 W high-pressure mercury lamp through a Pyrex jacket (Rikosangyo photochemical apparatus). After removing the solvent under reduced pressure, the residue was crystallized from ethanol to give *trans*-5-benzyl-6a,11b-dihydrobenzofuro[2,3-*c*]quinolin-6(5*H*)-one (**7**) (1.65 g, 82%) as pale yellow needles: mp 183—184 °C; IR 1710 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ=4.7 (2H, s, 6a-H and 11b-H), 5.2 (1H, d, *J*=16 Hz, NC$\underline{H}$HPh), 5.3 (1H, d, *J*=16 Hz, NCH$\underline{H}$Ph). This dihydrobenzofuroquinolinone **7** was dehydrogenated by refluxing with 5% palladium–carbon in decalin for 12 h. After cooling, the mixture was diluted with chloroform and filtered to remove the catalyst. After removing the solvent under reduced pressure, the residue was crystallized from ethanol to give 5-benzylbenzofuro[2,3-*c*]quinolin-6(5*H*)-one (**5b**) (260 mg, 65%) as colorless powder: mp 215—217 °C; IR 1660 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ=5.1 (2H, s, NCH_2Ph); Found: C, 81.48; H, 4.78; N, 4.34%; M^+, 325. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31%; M, 325. The benzylquinolinone **5b** (0.55 g, 1.7 mmol) was debenzylated by heating with methanesulfonic acid (8 ml) at ca. 125 °C for 5 h with stirring. After treating with ice-water, the precipitates were washed with chloroform and recrystallized from 2-ethoxyethanol to give **5a** (0.16 g, 40%), which was identical with the sample from **1** and ethyl bromoacetate of chloroacetonitrile, described above.

6-Chlorobenzofuro[2,3-*c*]quinoline (4b). To a solution of **5a** (0.54 g, 2.3 mmol) in phosphoryl chloride (25 ml) was added phosphorus pentachloride (0.47 g, 2.3 mmol); the mixture was heated under reflux for 2 h with stirring. After cooling, the mixture was poured into ice-water. The precipitates were recrystallized from ethanol to give 6-

chlorobenzofuro[2,3-*c*]quinoline (**4b**) (0.50 g, 86%) as colorless needles: mp 157.5—158.5 °C; UV 224sh (log ε 4.45), 237sh (4.66), 243 (4.74), 262 (3.82), 296sh (4.10), 309 (4.28), 323.5 (4.20), 336 nm (3.92); Found: C, 71.04; H, 3.04; N, 5.40; M^+, 253. Calcd for $C_{15}H_8ClNO$: C, 71.02; H, 3.18; N, 5.52%, M. 253.

6-Cyanobenzofuro[2,3-*c*]quinoline (4c). A mixture of **4b** (1.64 g, 6.47 mmol), sodium cyanide (0.51 g, 14 mmol), dry DMF (15 ml) was heated under reflux for 6 h. After cooling, the mixture was diluted with cold water, and the precipitates were treated well with chloroform. The precipitates, which were insoluble in chloroform, were recrystallized from ethanol to give quinolinone **5a** (0.04 g, 3%). The parts soluble in chloroform were chromatographed on a short silica-gel column to give 6-cyanobenzofuro[2,3-*c*]quinoline (**4c**) (0.45 g, 29%) as colorless needles and starting material **4b** (0.23 g, 15%). **4c**: mp 223—224 °C; UV 230sh (log ε 4.46), 245 (4.70), 276 (3.67), 328 (4.25), 348sh (3.95), 365 nm (3.88); Found: C, 78.40; H, 3.27; N, 11.25%; M^+, 244. Calcd for $C_{16}H_8N_2O$: C, 78.68; H, 3.30; N, 11.47%; M, 244.

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7) This compound was labile because of its partial autoxidation and therefore the elemental analysis was impossible.