The Synthesis of Benzofuroquinolines. VII. Some Benzo[*h*]benzofuro[2,3-*b*]- and [3,2-*c*]quinoline Derivatives

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Benzo[*h*]benzofuro[3,2-*c*]quinoline (**2a**) and its 6-methyl derivative **2b** were synthesized by the demethyl-cyclization of 3-(*o*-methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5a**) and its 2-methyl derivative **5b**. And, two benzo[*h*]benzofuro[2,3-*b*]- and [3,2-*c*]quinolinones **8** and **9** were synthesized by the demethyl-cyclization of 4-hydroxy-3-(*o*-methoxyphenyl)-2(1*H*)-benzo[*h*]quinolinone (**7**), and they were converted to the corresponding chloro derivatives **1c** and **2c** and benzo[*h*]benzofuro[2,3-*b*]quinoline-7-carbonitrile (**1d**).

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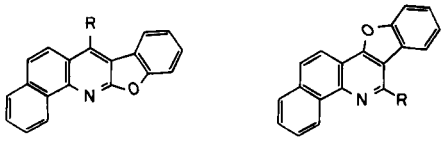
In the course of our studies of polycyclic heteroaromatic compounds, we studied the syntheses of benzofuroquinolines in order to investigate their chemical reactivities and also to test their activities as mutagens, carcinogens, and also antitumor substances. We already reported the syntheses of some benzofuro[2,3-*b*]-, [3,2-*b*]- and [3,2-*c*]quinolines in our previous paper [1]. In this paper, we describe the synthesis of some benzo[*h*]benzofuro[2,3-*b*]- and [3,2-*c*]-quinoline derivatives, having a structure similar to chrysene.

Chart 1



We already reported the synthesis of benzofuro[3,2-*c*]-quinoline and its 6-methyl derivative from aniline and ethyl 2-(*o*-methoxyphenyl)-3-oxopropanoate or 2-(*o*-methoxyphenyl)-3-oxobutyronitrile. Analogously, condensation of 1-naphthylamine with ethyl 2-(*o*-methoxyphenyl)-3-oxopropanoate (**3**) gave 3-(*o*-methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5a**), which was converted to benzo[*h*]benzofuro-[3,2-*c*]quinoline (**2a**) by the demethyl-cyclization with pyridine hydrochloride. Condensation of 1-naphthylamine with 2-(*o*-methoxyphenyl)-3-oxobutyronitrile (**4**) gave 2-methyl-3-(*o*-methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5b**), which was also converted to 6-methylbenzo[*H*]benzofuro[3,2-*c*]quinoline (**2b**) by the demethyl-cyclization. But, a similar preparation of **5b** failed in the condensation of 1-naphthylamine with ethyl 2-(*o*-methoxyphenyl)-3-oxobutyrate.

Chart 3

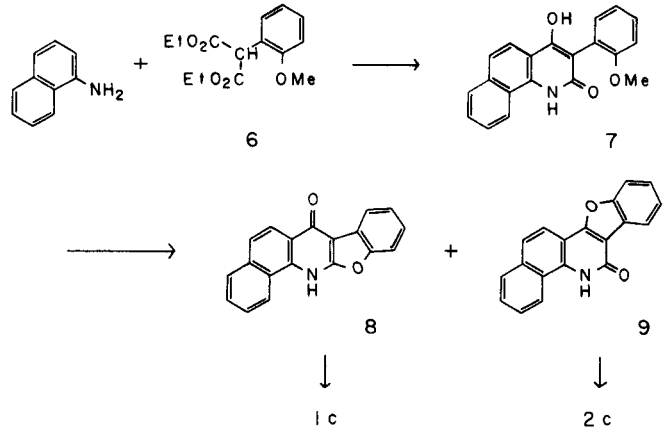
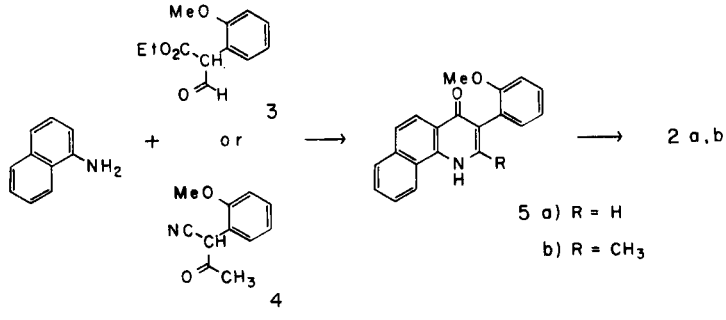


Chart 2



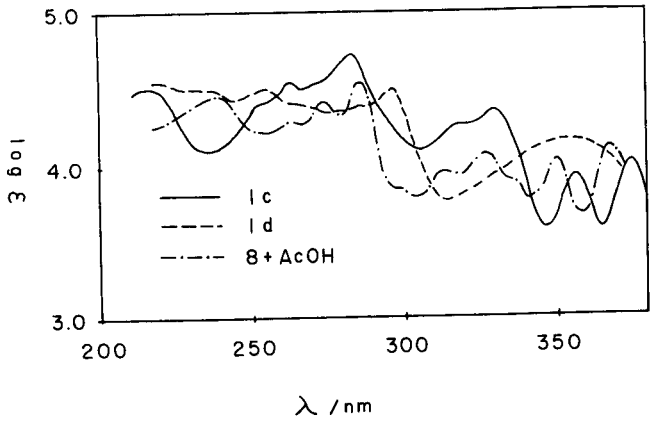


Figure 1. The uv spectra of benzo[*h*]benzofuro[2,3-*b*]quinoline derivatives **1c,d** and **8**.

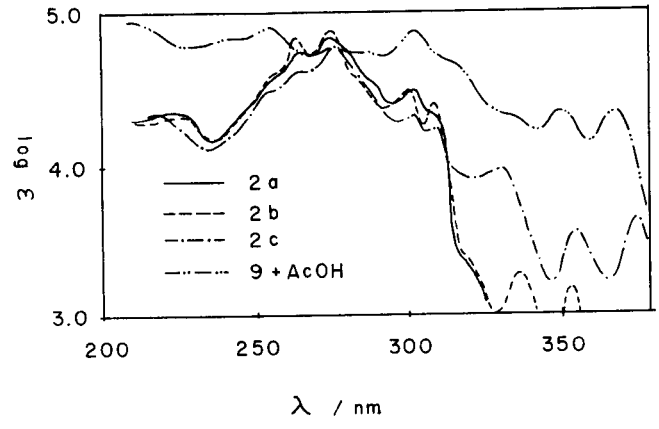


Figure 2. The uv spectra of benzo[*h*]benzofuro[3,2-*c*]quinoline derivatives **2a,b,c** and **9**.

We also reported the synthesis of two benzofuroquinolinones *via* 4-hydroxy-3-(*o*-methoxyphenyl)-2(1*H*)quinolinone and their conversion to the corresponding chlorobenzofuroquinolines [1b,d]. Analogous condensation of 1-naphthylamine with ethyl (*o*-methoxyphenyl)malonate (**6**) gave 4-hydroxy-3-(*o*-methoxyphenyl)-2(1*H*)-benzo[*h*]quinolinone (**7**). The demethyl-cyclization of **7** gave a mixture of two benzo[*h*]benzofuroquinolinones, alkaline soluble 7(13*H*)-benzo[*h*]benzofuro[2,3-*b*]quinolinone (**8**) and an alkaline insoluble 6(5*H*)-benzo[*h*]benzofuro[3,2-*c*]quinolinone (**9**), which were converted to the corresponding chloro derivatives **1c** and **2c** by chlorination with phosphorus pentachloride in phosphoryl chloride. The cyanation of both chlorides **1c** and **2c** with sodium cyanide gave the same linear cyanide, benzo[*h*]benzofuro[2,3-*b*]quinoline-7-carbonitrile (**1d**). It shows that a re-cyclization occured in this cyanation of the angular chloride **2c**; a cyanide ion probably attacked carbon 11b and a resulting phenoxide ion then attacked carbon 6. For an angular cyanide **2d**, we also tried another cyanation of **2c** with copper(I) cyanide, but only the starting chloride **2c** was recovered.

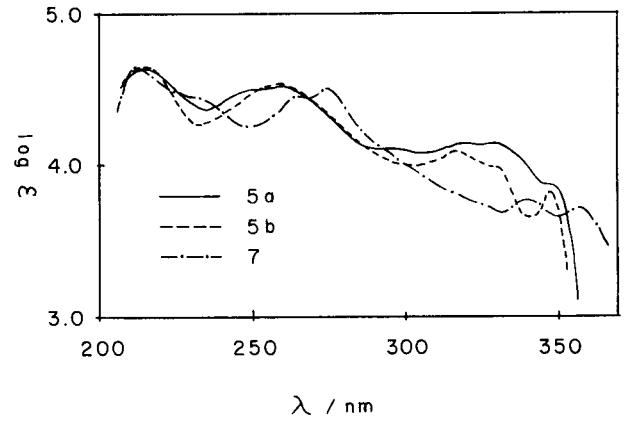


Figure 3. The uv spectra of the intermediate benzo[*h*]quinolinones **5a,b** and **7**.

EXPERIMENTAL

All melting points were determined on a micro melting point apparatus (Yanagimoto) or in a salt bath, and are uncorrected. The ir spectra were taken on a Hitachi EPI-S2 spectrophotometer

Table

Some Physical Data and Elemental Analyses of the New Compounds

Compound No.	Melting Point (°C)	IR (cm^{-1})	Mass (M^+) (m/z)	Elemental Analyses Found C(%)	Found H(%)	Found N(%)	Calcd. C(%)	Calcd. H(%)	Calcd. N(%)
1c	216-218	----	303	75.15	3.30	4.35	75.10	3.29	4.61 for $C_{19}H_{10}ClNO$
1d	266-273 dec	2300	294	81.54	3.37	9.62	81.60	3.40	9.52 for $C_{20}H_{10}N_2O$
2a	244-255.5	----	269	84.77	4.04	4.97	84.74	4.12	5.20 for $C_{19}H_{11}NO$
2b	210-210.5	----	283	84.87	4.59	4.92	84.78	4.53	4.94 for $C_{20}H_{13}NO$
5a	288.5-289.5	1640	301	79.50	5.11	4.36	79.71	5.02	4.65 for $C_{20}H_{15}NO_2$
5b	348-351 dec	----	315	79.70	5.29	4.18	79.98	5.43	4.44 for $C_{21}H_{17}NO_2$
7	314-317	1630	317	75.42	4.65	4.14	75.69	4.76	4.41 for $C_{20}H_{15}NO_3$
8	283-285 [a]	1645	285	72.84	4.36	3.88	73.03	4.38	4.06 for $C_{19}H_{11}NO_2$ + AcOH [a]
9	320-322	1650	285	72.89	4.31	3.82	73.03	4.38	4.06 for $C_{19}H_{11}NO_2$ + AcOH [a]

[a] Containing one molar acetic acid as solvent of crystallization.

as potassium bromide disks, and the uv spectra were taken on a Hitachi 220A spectrophotometer in ethanolic solutions. Mass spectra were recorded on a JEOL LMS-OISG-2 mass spectrometer. The physical data and elemental analyses are summarized in the Table and the uv data are summarized in Figures 1-3.

3-(*o*-Methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5a**).

According to the procedure reported in our previous paper [1a], a mixture of 1-naphthylamine (2.40 g, 16.8 mmoles) and ethyl 2-(*o*-methoxyphenyl)-3-oxopropanoate (**3**) (3.7 g, 16.7 mmoles) was allowed to stand at room temperature for a day to form an anil derivative, which was vigorously refluxed in diphenyl ether (6 g) for 3 hours. After cooling the mixture, the precipitates were collected. The filtrate was diluted with ether, and the ether layer was extracted with 5% sodium hydroxide solution. Acidification of the alkaline extracts with 10% hydrochloric acid also gave some precipitates. The combined precipitates were recrystallized from ethanol to give 3-(*o*-methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5a**) (1.40 g, 51%).

2-Methyl-3-(*o*-methoxyphenyl)-4(1*H*)-benzo[*h*]quinolinone (**5b**).

According to the procedure reported in our previous paper [1a], a mixture of 1-naphthylamine (2.30 g, 16.1 mmoles), 2-(*o*-methoxyphenyl)-3-oxobutyronitrile (**4**) (2.50 g, 13.2 mmoles), and polyphosphoric acid (n = 2.5) (18 g) was heated at *ca.* 100° for 30 minutes and at *ca.* 140° for 30 minutes. After cooling, the mixture was treated with dilute hydrochloric acid and neutralized to *ca.* *p*H 5 with 5% sodium hydroxide solution. The precipitates were recrystallized from acetic acid to give 2-methyl-3-(*o*-methoxyphenyl)-4(1*H*)-quinolinone (**5b**) (660 mg, 16%); ^{1}H nmr (trifluoroacetic acid): 2.8 ppm (3H, s).

Demethyl-cyclization of **5a,b** to Benzo[*h*]benzofuro[3,2-*c*]quinolines **2a,b**.

4(1*H*)-Benzo[*h*]benzofuro[3,2-*c*]quinolinones **2a,b** were vigorously refluxed with 10 parts of pyridine hydrochloride for 1.5 hours. After cooling, the mixture was treated with water and the precipitates were recrystallized from benzene for **2a** or from chloroform for **2b** to give benzo[*h*]benzofuro[3,2-*c*]quinoline (**2a**) in 70% yield and its 6-methyl derivative **2b** in 72% yield; ^{1}H nmr of **2b** showed a methyl singlet signal at 3.5 ppm in trifluoroacetic acid.

4-Hydroxy-3-(*o*-methoxyphenyl)-2(1*H*)-benzo[*h*]quinolinone (**7**).

According to the procedure reported in our previous paper [1c,d], a mixture of 1-naphthylamine (7.53 g, 52.6 mmoles), ethyl (*o*-methoxyphenyl)malonate (15.4 g, 57.9 mmoles), and diphenyl ether (28 g) was vigorously refluxed for 1 hour. After cooling, the mixture was diluted with diethyl ether and extracted with 5% sodium hydroxide solution. The alkaline layer was washed well with diethyl ether and then acidified with 10% hydrochloric acid. The precipitates were recrystallized from acetic acid to give 4-hydroxy-3-(*o*-methoxyphenyl)-2(1*H*)-quinolinone (**7**) (16.1 mmoles, 96%).

Demethyl-cyclization of **7**.

According to the procedure reported in our previous paper [1b], a mixture of **7** (1.58 g, 4.99 mmoles) and pyridine hydrochloride (16.0 g) was vigorously refluxed for 1.5 hours. After cooling, the mixture was treated with water. The precipitates were collected and then treated with 5% sodium hydroxide solution. The alkaline soluble parts were acidified with 10% hydrochloric acid and the precipitates were recrystallized from acetic acid to give 7(13*H*)-benzo[*h*]benzofuro[2,3-*b*]quinolinone (**8**) containing one mole acetic acid (288 mg, 17%). The alkaline insoluble precipitates were recrystallized from acetic acid to give 6(5*H*)-benzo[*h*]benzofuro[3,2-*c*]quinolinone (**9**) containing one mole acetic acid (1.05 g, 61%).

Conversion of **8** or **9** to Chlorobenzo[*h*]benzofuroquinolines **1c** or **2c**.

According to the procedure reported in our previous paper [1b,d], a mixture of **8** or **9** both containing one mole of acetic acid (*ca.* 4 mmoles), phosphorus pentachloride (*ca.* 5 mmoles), and phosphoryl chloride (16 ml) was refluxed for 2 hours with stirring. After cooling, the mixture was carefully treated with ice-water. The precipitates were recrystallized from cyclohexane to give the corresponding chlorides, 7-chlorobenzo[*h*]benzofuro[2,3-*b*]quinoline (**1c**) (66%) and 6-chlorobenzo[*h*]benzofuro[3,2-*c*]quinoline (**2c**) (77%).

Benzo[*h*]benzofuro[2,3-*b*]quinoline-7-carbonitrile (**1d**).

According to the procedure reported in our previous paper [1b], a mixture of **1c** (673 mg, 2.22 mmoles), sodium cyanide (*ca.* 200 mg, *ca.* 4 mmoles), and DMF (9 ml) was refluxed for 6 hours. After cooling, the mixture was treated with water, and the precipitates were recrystallized from cyclohexane-benzene (2:1) to give benzo[*h*]benzofuro[2,3-*b*]quinoline-7-carbonitrile (**1d**) (408 mg, 63%). Similar treatment of **2c** (993 mg, 3.27 mmoles) with sodium cyanide (*ca.* 300 mg, *ca.* 6 mmoles) in refluxing DMF (12 ml) also gave **1d** (204 mg, 21%).

REFERENCES AND NOTES

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