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The Synthesis of Benzofuroquinolines. II. Two Benzofuroquinolinones and Some Benzofuroquinoline Derivatives

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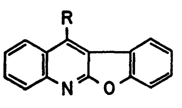
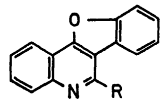
Two benzofuroquinolinones, 6,11-dihydrobenzofuro[2,3-*b*]quinolin-11-one and 5,6-dihydrobenzofuro[3,2-*c*]quinolin-6-one, were obtained by the demethyl-cyclization of 4-hydroxy-3-(*o*-methoxyphenyl)-1,2-dihydroquinolin-2-one. The chlorination of these benzofuroquinolinones afforded the corresponding chlorobenzofuroquinolines which were then converted to the cyanobenzofuroquinolines. The linear chlorobenzofuroquinoline was converted to 11-methoxy- and 11-ethoxybenzofuro[2,3-*b*]quinolines, and the linear cyanobenzofuroquinoline to benzofuro[2,3-*b*]quinoline-11-carboxylic acid and -11-carboxamide. The linear benzofuroquinolines thus obtained were oxidized to the corresponding *N*-oxides.

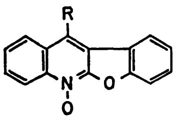
In the course of our studies of polycyclic heteroaromatics, we studied the synthesis of benzofuroquinolines in order to investigate their chemical reactivities and also to test their activities as mutagens, carcinogens, and also as anti-tumor substances. In a previous paper,1) we reported the synthesis of benzofuro[2,3-*b*]quinoline, benzofuro[3,2-*c*]quinoline, and their methyl, styryl, and carboxy derivatives. Mohanty *et al.*2) reported the synthesis of benzofuro[2,3-*b*]quinolin-11-ol (**1a**) by the condensation of anthranilic acid and 2(3*H*)-benzofuranone. However, they showed a very low melting point of 93—95 °C compared to those of our reported1) benzofuroquinolines, and also had ambiguous elemental analysis data; Found: C, 75.95; H, 3.80%. Calcd for $C_{15}H_9NO_2$: C, 76.60; H, 3.83%. We checked this condensation reaction, but could not obtained the same compound. Therefore, in this paper, we will report the synthesis of two benzofuroquinolinones (corresponding to benzofuroquinolinols) and their conversion to chloro- and cyanobenzofuroquinolines.



1 a–g



2 a–c



3 b,c

a) R = OH
b) R = Cl
c) R = CN
d) R = OMe
e) R = OEt
f) R = CO_2H
g) R = $CONH_2$

Chart 1.

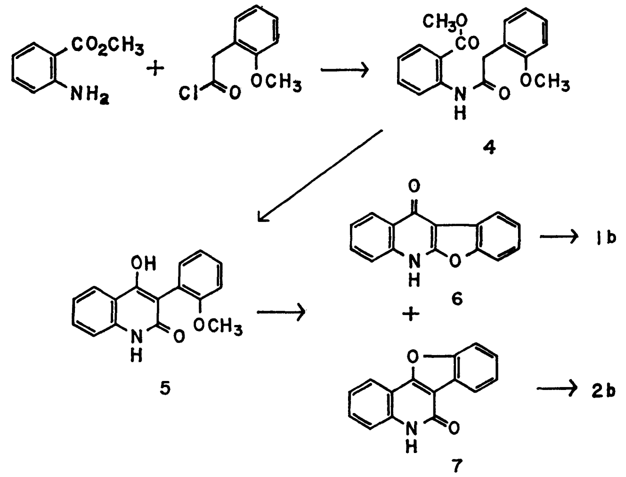


Chart 2.

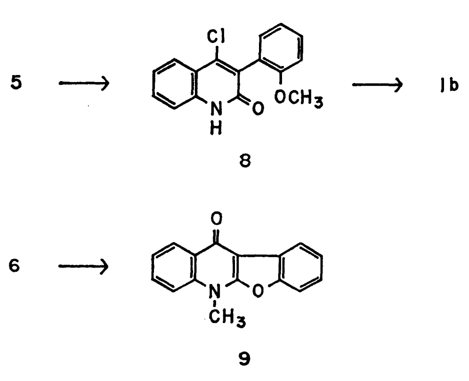


Chart 3.

4-Hydroxy-3-(*o*-methoxyphenyl)-1,2-dihydroquinolin-2-one (**5**) was prepared according to the reported procedure.1) The amide (**4**), prepared from *o*-methoxyphenylacetyl chloride and methyl anthranilate, was cyclized to a hydroxyquinolinone (**5**) by the action of sodium hydroxide. The demethyl-cyclization of **5** by heating with pyridine hydrochloride furnished a mixture of two benzofuroquinolinones, an alkali-soluble benzofuroquinolinone (**6**) and an alkali-insoluble benzofuroquinolinone (**7**). These benzofuroquinolinones were converted to the corresponding chlorobenzofuroquinolines (**1b** and **2b**) by chlorination with phosphorus pentachloride in phosphoryl chloride. In the UV spectra, 4,5-dihydrofuro[3,2-*c*]quinolin-4-one3) corresponded to the benzofuroquinolinone (**7**) more than to the benzofuroquinolinone (**6**) (Fig. 1); the chlorobenzofuroquinoline (**1b**) derived from **6** was similar to linear benzofuro[2,3-*b*]quinoline,1) and the chlorobenzofuroquinoline (**2b**) was similar to angular benzofuro[3,2-*c*]quinoline1) (Fig. 2). These facts show that the benzofuroquinolinone (**6**) was linear 6,11-dihydrobenzofuro[2,3-*b*]quinolin-11-one with a quinolinol tautomerism, while the benzofuroquinolinone (**7**) was angular 5,6-dihydrobenzofuro[3,2-*c*]quinolin-6-one. The linear chlorobenzofuroquinoline (**1b**) was also obtained from **5** *via* 4-chloro-3-(*o*-methoxyphenyl)-1,2-dihydroquinolin-2-one (**8**) by monochlorination,

TABLE 1. ELEMENTAL ANALYSES OF NEW COMPOUNDS

Compound	Found C(%)	Found H(%)	Found N(%)	Formula	Calcd C(%)	Calcd H(%)	Calcd N(%)
1b	71.00	2.98	5.49	$C_{15}H_8ClNO$	71.02	3.18	5.52
1c	78.84	3.35	11.53	$C_{16}H_8N_2O$	78.69	3.28	11.48
1d	76.88	4.30	5.42	$C_{16}H_{11}NO_2$	77.09	4.45	5.62
1e	77.78	4.98	5.52	$C_{17}H_{13}NO_2$	77.55	4.98	5.32
1g	73.53	3.81	10.47	$C_{16}H_{10}N_2O_2$	73.27	3.84	10.68
2b	70.74	3.02	5.37	$C_{15}H_8ClNO$	71.02	3.18	5.52
2c	78.72	3.08	11.44	$C_{16}H_8N_2O$	78.69	3.28	11.48
3b	66.58	2.91	4.98	$C_{15}H_8ClNO_2$	66.85	2.99	5.20
3c	73.75	2.81	10.47	$C_{16}H_8N_2O_2$	73.84	3.10	10.77
4	68.05	5.75	4.69	$C_{17}H_{17}NO_4$	68.21	5.73	4.68
5	71.76	4.97	4.96	$C_{15}H_{13}NO_3$	71.90	4.90	5.24
6	76.55	3.75	5.69	$C_{15}H_9NO_2$	76.58	3.86	5.96
7	76.30	3.65	5.95	$C_{15}H_9NO_2$	76.58	3.86	5.96
8	67.50	4.02	4.78	$C_{16}H_{12}ClNO_2$	67.25	4.20	4.90
9	76.96	4.38	5.86	$C_{16}H_{11}NO_2$	77.09	4.45	5.62

TABLE 2. THE UV SPECTRAL DATA OF BENZOFUROQUINOLINE DERIVATIVES

Compound	λ_{max} (log ε) (nm)
1c	222(4.65) 262(4.64) 277sh(3.99) 349(4.33) 366(4.35)
1d	222(4.59) 250(4.69) 258(4.86) 274.5(3.87) 287sh(3.80) 304sh(4.18) 316(4.36) 330(4.18) 342sh(3.81)
1e	222(4.59) 250(4.70) 258(4.86) 274.5(3.93) 287sh(3.89) 305sh(4.17) 317(4.33) 330(4.15) 342sh(3.80)
1g	221(4.67) 250sh(4.57) 258(4.73) 325(4.34) 339sh(4.26)
2c	211(4.36) 229(4.32) 257sh(4.66) 265(4.70) 286(4.26) 298(4.14) 348(3.52) 360(3.50)
3b	224.5(4.42) 259(4.63) 267(4.65) 291sh(4.12) 325(4.11) 340(4.16)
3c	210.5(4.45) 233sh(4.27) 270(4.47) 362(4.16)
9	222(4.49) 258sh(4.49) 265(4.62) 288(4.00) 302(3.94) 326(4.03) 339(4.08) 356(3.81)

sh: shoulder

followed by demethyl-cyclization. The linear benzofuroquinolinone (**6**) gave 6-methyl-6,11-dihydrobenzofuro[2,3-*b*]quinolin-11-one (**9**) by *N*-methylation with methyl iodide. 11-Cyano-, 11-methoxy-, and 11-ethoxybenzofuro[2,3-*b*]quinolines (**1c**, **d**, **e**) were obtained from **1b** by means of nucleophilic substitution reactions with sodium cyanide, methanol–sodium hydroxide, and ethanol–sodium hydroxide, respectively. The acid hydrolysis of **1c** gave benzofuro[2,3-*b*]quinoline-11-carboxylic acid (**1f**), and the alkaline hydrolysis of **1c** in ethanol gave benzofuro[2,3-*b*]quinoline-11-carboxamide (**1g**). However, the alkaline hydrolysis of **1b** and **1c** in dimethyl sulfoxide gave a mixture of two benzofuroquinolinones (**6** and **7**). The cyanation of angular **2b** with sodium cyanide afforded linear **1c**, but this cyanation to angular 6-cyanobenzofuro[3,2-*c*]quinoline (**2c**) was effected with copper(I) cyanide. The benzofuroquinolines (**1b**, **c**) thus obtained were converted to the corresponding *N*-oxides (**3b**, **c**) by *N*-oxidation with trifluoroperacetic acid, but the

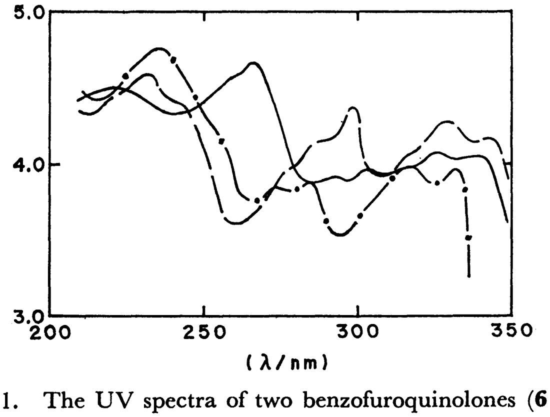


Fig. 1. The UV spectra of two benzofuroquinolones (**6** and **7**) and 4,5-dihydrofuro[3,2-*c*]quinolin-4-one.[3]
——: **6**, — —: **7**, —·—: 4,5-dihydrofuro[3,2-*c*]quinolin-4-one.

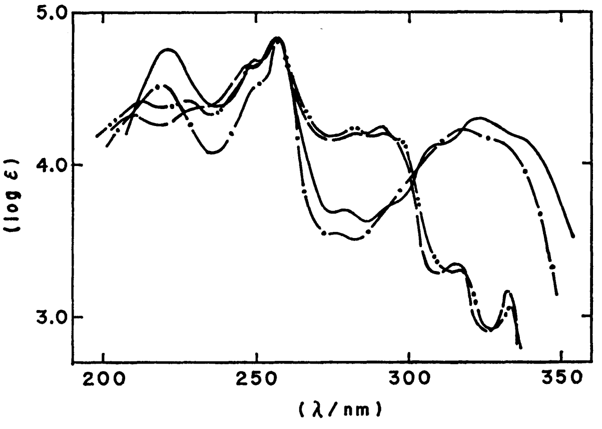


Fig. 2. The UV spectra of two chlorobenzofuroquinolines (**1b** and **2b**), linear benzofuro[2,3-*b*]quinoline,[1] and angular benzofuro[3,2-*c*]quinoline.[1]

N-oxidation of the angular benzofuroquinolines (**2b**, **c**) was unsuccessful under these conditions.

Compounds (**5**), (**7**), and (**8**) seem to possess 2-quinolone structures principally, since they have ν_{co} bands around 1650 cm^{-1} in their IR spectra. In both the IR and UV spectra, compound (**6**) was similar to 6-methyl-6,11-dihydrobenzofuro[2,3-*b*]quinolin-11-one (**9**), not to 6-methoxybenzofuro[2,3-*b*]quinoline (**1d**). This evidence shows that compound (**6**) has mainly a benzofuroquinolinone, not a benzofuroquinolinol, structure.

Experimental

The melting points have not been corrected; the mass spectra were measured on a JEOL JMS-OISG-2 mass spectrometer, the IR spectra, on a Hitachi EPI-S2 spectrophotometer, and the UV spectra, on a Hitachi 124 spectrophotometer in an ethanol solution. The UV and elemental analyses data are summarized in the figures and the tables.

N-(*o-Methoxycarbonylphenyl*)*-o-methoxyphenylacetamide (4).* *o*-Methoxyphenylacetyl chloride (prepared from 25 g of *o*-methoxyphenylacetic acid and thionyl chloride) was added to a solution of methyl anthranilate (23 g) in pyridine (50 ml), after which, the mixture was refluxed for 1 h with stirring. The cooled reaction mixture was treated with water. The resulting precipitates were collected and recrystallized from ethyl acetate to give 34 g (75%) of **4** as colorless crystals; mp 116—117 °C; IR (KBr); 1710 and 1680 cm^{-1}.

*4-Hydroxy-3-(*o*-methoxyphenyl)-1,2-dihydroquinolin-2-one (5).* A mixture of **4** (34 g), sodium methylate (prepared from 10 g of sodium metal and absolute methanol), and dry benzene (210 ml) was refluxed for 6 h. The cooled reaction mixture was treated with water. The aqueous layer was acidified with dilute hydrochloric acid. The resulting precipitates were collected and recrystallized from *N*,*N*-dimethylformamide to give 31 g (80%) of **5** as colorless crystals; mp 311—312 °C; IR (KBr): 1645 cm^{-1}.

Demethyl-cyclization of 5. A mixture of **5** (2.6 g) and anhydrous pyridine hydrochloride (26 g) (bp 218 °C) was refluxed vigorously for 1.5 h. The cooled reaction mixture was treated with water, and the resulting precipitates were collected. Then the precipitates were treated with a 5% sodium hydroxide aqueous solution and filtered. The remaining precipitates were crystallized from ethanol to give 0.52 g (21%) of **7** as colorless crystals; mp 294—296 °C; MS (M$^+$): 235; IR (KBr): 1670 cm^{-1}. The filtrate was acidified with dilute hydrochloric acid, and the resulting precipitates were collected and recrystallized from ethanol to give 1.54 g (63%) of **6** as colorless needles; mp 342—344 °C (dec); MS (M$^+$): 235; IR (KBr): 1655 cm^{-1}.

*11-Chlorobenzofuro[2,3-*b*]quinoline (1b).* A mixture of **6** (3.9 g), phosphoryl chloride (23 ml), and phosphorus pentachloride (4.3 g) was refluxed for 2 h. The cooled reaction mixture was treated with water, and the resulting white precipitates were recrystallized from ethanol to give 3.6 g (85%) of **1b** as colorless crystals; mp 211—212 °C; MS (M$^+$): 253.

*6-Chlorobenzofuro[3,2-*c*]quinoline (2b).* By a method similar to that described for **1b**, a mixture of **7** (4.2 g), phosphorus pentachloride (4.6 g), and phosphoryl chloride (25 ml) afforded the crude chloride, which was recrystallized from ethanol to give 4.1 g (91%) of **2b** as colorless crystals; mp 157.5—158.5 °C; MS (M$^+$): 253.

*11-Cyanobenzofuro[2,3-*b*]quinoline (1c).* A mixture of **1b** (2.0 g), sodium cyanide (0.5 g), and *N*,*N*-dimethylformamide (30 ml) was refluxed for 6 h. The cooled reaction mixture was treated with water. The resulting precipitates were collected and recrystallized from ethanol to give 1.6 g (82%) of **1c** as colorless crystals; mp 242—243 °C; MS (M$^+$): 244; IR (KBr): 2230 cm^{-1}. Under these cyanation condition, 1c was also obtained from the angular chloride (**2b**) in a 72% yield.

*6-Cyanobenzofuro[3,2-*c*]quinoline (2c).* A mixture of **2b** (0.5 g), copper(I) cyanide (0.3 g), and *N*,*N*-dimethylformamide (5 ml) was refluxed for 6 h. The cooled reaction mixture was treated with ethylenediamine (10 ml) and water and extracted with diethyl ether. The ether layer was washed with a 10% sodium cyanide aqueous solution, filtered, washed with water, and dried over anhydrous sodium sulfate. The residue from the evaporation of the ether was crystallized from ethanol to give 0.1 g (21%) of **2c** as colorless crystals; mp 182—184 °C; MS (M$^+$): 244; IR (KBr): 2230 cm^{-1}.

Monochlorination of 6. A mixture of **6** (2.0 g), phosphorus pentachloride (2.0 g), and phosphoryl chloride (30 ml) was refluxed for 2 h. A treatment similar to that described for **1b** afforded white precipitates, which were recrystallized from methanol to give 0.95 g (44%) of **8** as colorless crystals; mp 101—103 °C; IR (KBr): 1640 cm^{-1}.

Demethyl-cyclization of 8. A mixture of **8** (0.55 g) and anhydrous pyridine hydrochloride (5.5 g) was refluxed for 1.5 h; this afforded 0.28 g (14%) of **1b** (mp 211—212 °C), which was identified with a sample obtained by the chlorination of **6**.

N-*Methylation of 6 to 9.* A mixture of **6** (0.5 g), sodium hydroxide (1.0 g), methyl iodide (1.3 g), and ethanol (30 ml) was refluxed for 3 h. After cooling, the reaction mixture was treated with dilute hydrochloric acid and filtered. The resulting precipitates were collected and recrystallized from ethanol to give 0.34 g (64%) of **9** as dark silky needles; mp 360—362 °C; MS (M$^+$): 249; IR (KBr): 1660 cm^{-1}.

*11-Methoxy- and 11-Ethoxybenzofuro[2,3-*b*]quinolines (1d,e).* A mixture of **1a** (0.53 g), potassium hydroxide (0.3 g), and methanol (15 ml) was refluxed for 2 h. The cooled reaction mixture was treated with water. The resulting precipitates were collected and recrystallized from cyclohexane to give 0.33 g (64%) of **1d** as a colorless powder; mp 165—165.5 °C; MS (M$^+$): 249. Similarly, **1b** afforded **1e** as a powder in a 23% yield; mp 72—73 °C; MS (M$^+$): 263.

Acid Hydrolysis of 1c. The linear cyano derivative (**1c**) (0.51 g) was suspended in 20 ml of 70% aqueous sulfuric acid. The mixture was refluxed for 3 h, and then treated with cold water. The resulting precipitates were collected and recrystallized from ethanol to give benzofuro[2,3-*b*]quinoline-11-carboxylic acid (**1f**); mp 326 °C (dec), as reported in the previous paper.[1)]

Alkaline Hydrolysis of 1c. A mixture of **1c** (0.80 g), a 50% potassium hydroxide aqueous solution (1 ml), and ethanol (20 ml) was refluxed for 3 h. The resulting precipitates were collected and recrystallized from ethanol to give 0.32 g (38%) of benzofuro[2,3-*b*]quinoline-11-carboxamide (**1g**); mp 265—266 °C; MS (M$^+$): 262; IR (KBr): 1660 cm^{-1}. However, the similar hydrolysis in dimethyl sulfoxide converted **1c** to a mixture of **6** and **7** in 19 and 20% yields respectively.

Alkaline Hydrolysis of 1b. A mixture of **1b** (1.0 g), a 50% potassium hydroxide aqueous solution (20 ml), and dimethyl sulfoxide (10 ml) was refluxed for 3 h. After a treatment similar to that described for the demethyl-cyclization of **5**, 0.40 g (43%) of **6** and 0.17 g (19%) of **7** were obtained.

N-*Oxidation of 1b and 1c.* To a solution of **1b** (1.0 g) in trifluoroacetic acid (6 ml), a 30% hydrogen peroxide aqueous solution (0.7 ml) was added, after which the mixture was heated at 60—70 °C for 3 h. The heating was continued at the same temperature for 6 additional hours with the addition of more of the 30% hydrogen peroxide aqueous solution (0.4 ml). The reaction mixture was then concentrated under reduced pressure and neutralized with a sodium carbonate aqueous solution. The resulting precipitates were collected and recrystallized from ethanol to give 0.63 g (59%) of **3b** as dark yellow needles; mp 257—259 °C; MS (M^+): 269. Similarly, **1c** (1.0 g) was oxidized to **3c** (0.52 g, 49%); mp 259.5—261 °C (from ethanol); MS (M^+): 260; IR (KBr): 2230 cm^{-1}.

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