The Synthesis of Benzofuroquinolines. VIII. Some Halobenzofuro[2,3-*c*]quinoline Derivatives

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Three 2-halo-6(5*H*)-benzofuro[2,3-*c*]quinolinones **1** (X = F, Cl, Br) were synthesized in two procedures, photocyclization of *N*-benzyl-*N*-(*p*-halophenyl)-2-benzofurancarboxamides **3** (X = F, Cl, Br) and condensation of 2-amino-2'-hydroxybenzophenones **7** (X = F, Cl, Br) with chloroacetonitrile. Three 2-halo-6-methylbenzofuro[2,3-*c*]quinolines **2** (X = F, Cl, Br) were also synthesized by the condensation of 2-amino-5-halo-2'-hydroxybenzophenones **7** (X = F, Cl, Br) with chloroacetone.

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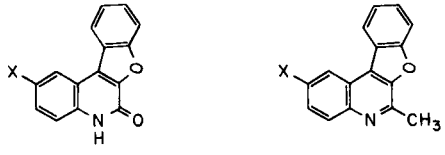
In the course of our studies of polycyclic heteroaromatic compounds, we studied the syntheses of benzofuroquinolines in order to investigate their chemical reactivities and also to test their activities as mutagens, carcinogens, and also antitumor substances. In our previous paper [1], we reported a new approach to benzofuro[2,3-*c*]quinoline derivatives. By Frier *et al.* [2], a halo derivative of structurally similar indolo[2,3-*c*]quinolinone, 10-chloro-5-[2-(dimethylamino)ethyl]-5,6-dihydro-6-indolo[2,3-*c*]quinolinone, showed a powerful antitumor activity. So, in this paper, we report the synthesis of 2-halobenzofuro[2,3-*c*]-quinoline derivatives.

Chart 1

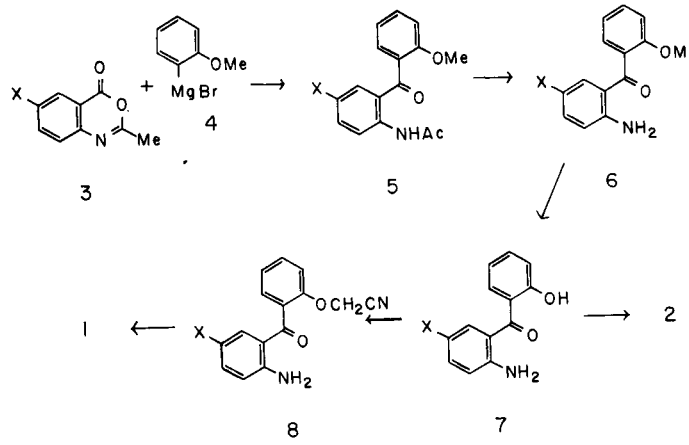


1 2

We already reported the synthesis of 6(5*H*)-benzofuro-[2,3-*c*]quinolinone (**1**, X = H) and 6-methylbenzofuro-[2,3-*c*]quinoline (**2**, X = H) from 2-amino-2'-hydroxybenzophenone (**7**, X = H) [1]. Similarly, 6-halo-2-methyl-3,1-benzooxazepin-4-ones **3** (X = F, Cl, Br) was prepared from the corresponding 5-haloanthranilic acids and acetic anhydride. The Grignard condensation of **3** (X = F, Cl, Br) with *o*-methoxyphenylmagnesium bromide gave 2-acetamino-4-halo-2'-methoxybenzophenones **5** (X = F, Cl, Br), which were converted to our key intermediates, 2-amino-4-halo-2'-hydroxybenzophenones **7** (X = F, Cl, Br) by the hydrolysis of **5** (X = F, Cl, Br) to **6** (X = F, Cl, Br) with refluxing ethanolic hydrochloric acid followed by the demethylation of **6** (X = F, Cl, Br) with anhydrous aluminium chloride.

The condensation of **7** (X = F, Cl, Br) with chloroacetonitrile gave the corresponding 2-(2-amino-4-halobenzoyl)-phenyloxyacetonitriles **8** (X = F, Cl, Br) after refluxing

Chart 2



3 4 5 6 7 8

with potassium carbonate in acetone for 4 hours. This nitrile **8** (X = F, Cl, Br) was effectively converted to the corresponding 2-halo-6(5*H*)-benzofuro[2,3-*c*]quinolinones **1** (X = F, Cl, Br) by refluxing with potassium hydroxide in 2-ethoxyethanol for 6 hours. The condensation of **7** (X = F, Cl, Br) with chloroacetone gave 2-halo-6-methylbenzofuro[2,3-*c*]quinolines **2** (X = F, Cl, Br) directly after refluxing with potassium carbonate in acetone for 4.5 hours.

Photo-irradiation of *N*-(4-halophenyl)-2-benzofurancarboxamides **9** (X = F, Cl, Br), prepared from 2-benzofurancarbonyl chloride and the corresponding *N*-benzyl-4-haloaniline, was attempted. Photocyclization of a fluoro derivative **9** (X = F) gave 5-benzyl-2-fluoro-6a,11b-dihydro-6(5*H*)-benzofuro[2,3-*c*]quinolinone (**10**, X = F) after a long uv irradiation. While, in similar photocyclizations,

Chart 3

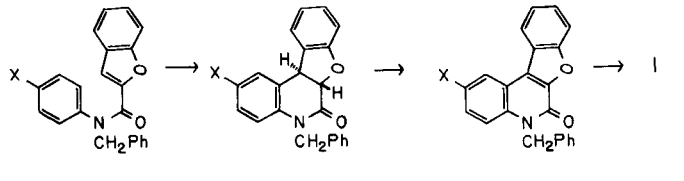


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Table

Some Physical Data and Elemental Analyses of the New Compounds

Compound No.	X	Melting Point (°C)	IR (υCO) (cm^{-1})	Mass (M^+) (m/z)	Elemental Analyses Found C(%)	Found H(%)	Found N(%)	Calcd. C(%)	Calcd. H(%)	Calcd. N(%)
1	F	345-346	1690	253	71.38	3.32	5.46	71.15	3.18	5.53 for $C_{15}H_{18}FNO_2$
1	Cl	370-371	1680	269, 271	67.03	3.05	5.14	66.80	2.99	5.19 for $C_{15}H_{18}ClNO_2$
1	Br	322-324	1680	313, 135	57.10	2.70	4.45	57.34	2.57	4.46 for $C_{15}H_{18}BrNO_2$
2	F	141.5-142	----	251	76.30	3.94	5.50	76.48	4.01	5.57 for $C_{16}H_{10}FNO$
2	Cl	192.5-193.5	----	267, 269	71.96	3.77	5.18	71.78	3.77	5.23 for $C_{16}H_{10}ClNO$
2	Br	199.5-200	----	311, 313	61.56	3.23	4.49	61.59	3.15	4.49 for $C_{16}H_{10}BrNO$
5	F	146-146.5	1635, 1690	187	66.84	4.96	4.82	66.89	4.91	4.88 for $C_{16}H_{14}FNO_3$
5	Cl	132-133	1645, 1700	303, 305	63.44	4.49	4.86	63.27	4.65	4.61 for $C_{16}H_{14}ClNO_3$
5	Br	139-140	1640, 1695	347, 349	55.27	4.10	3.98	55.19	4.05	4.02 for $C_{16}H_{14}BrNO_3$
6	F	106.5-107	1620	245	68.41	4.95	5.74	68.56	4.93	5.71 for $C_{14}H_{12}FNO_2$
6	Cl	86.5-87	1615, 1630	261, 263	64.23	4.71	5.48	64.25	4.62	5.35 for $C_{14}H_{12}ClNO_2$
6	Br	90-91	1615, 1630	305, 307	55.22	4.00	4.38	54.92	3.95	4.58 for $C_{14}H_{12}BrNO_2$
7	F	91.5-92	1625	231	67.27	4.43	6.07	67.53	4.36	6.06 for $C_{13}H_{18}FNO_2$
7	Cl	101.5-102	1605	247, 249	63.07	4.15	5.49	63.04	4.07	5.66 for $C_{13}H_{18}ClNO_2$
7	Br	77-78	1605	291, 293	55.37	3.36	5.01	55.45	3.45	4.80 for $C_{13}H_{18}BrNO_2$
8	F	107-107.5	1630	270	66.73	4.04	10.22	66.66	4.10	10.37 for $C_{15}H_{11}FN_2O_2$
8	Cl	129-130	1620	286, 288	62.55	3.85	9.81	62.84	3.87	9.77 for $C_{15}H_{11}ClN_2O_2$
8	Br	115-116	1625	330, 332	54.32	3.32	8.52	54.40	3.35	8.46 for $C_{15}H_{11}BrN_2O_2$
10	F	192-196	1695	345	76.52	4.48	4.29	76.51	4.67	4.06 for $C_{22}H_{16}FNO_2$
10	Cl	228-234	1690	361, 363	73.12	4.38	3.89	73.03	4.46	3.87 for $C_{22}H_{16}ClNO_2$
11	F	258-260	1665	343	76.88	4.22	3.88	76.96	4.11	4.08 for $C_{22}H_{14}FNO_2$
11	Cl	282-285	1670	359, 361	73.70	4.17	3.98	73.44	3.92	3.89 for $C_{22}H_{14}ClNO_2$
11	Br	287-288	1660	403, 405	65.36	3.49	3.46	65.59	3.55	3.46 for $C_{22}H_{14}BrNO_2$

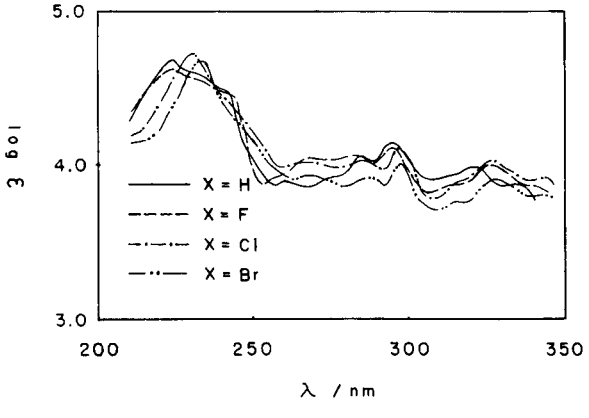

Figure 1. The uv spectra of 6(5*H*)-benzofuro[2,3-*c*]quinolinones.

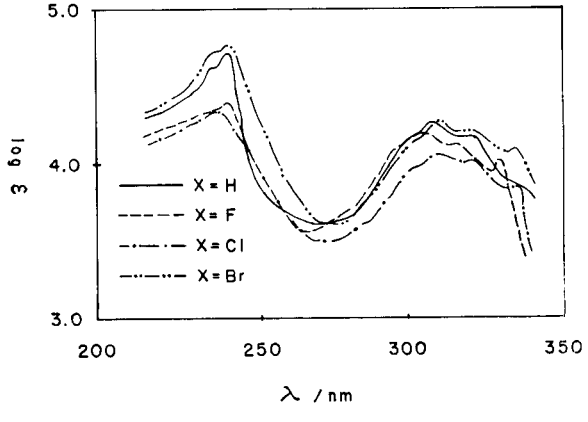

Figure 2. The uv spectra of 6-methylbenzofuro[2,3-*c*]quinolines.

a chloro derivative **9** (X = Cl) gave a mixture of cyclized **10** (X = Cl) and further dehydrogenated **11** (X = Cl), and a bromo derivative gave dehydrogenated **11** (X = Br) only. These dihydrobenzofuro[2,3-*c*]quinolinones **10** (X = F, Cl) were readily dehydrogenated to the corresponding 5-benzyl-2-halo-6(5*H*)-benzofuro[2,3-*c*]quinolinones **11** (X = F, Cl) by refluxing with 5% palladium-carbon in decalin. The debenzylation of 5-benzyl-2-halo-6(5*H*)-benzofuro-[2,3-*c*]quinolinones **11** (X = F, Cl, Br) gave 2-halo-6(5*H*)-benzofuro[2,3-*c*]quinolinones **1** (X = F, Cl, Br) after heating with methanesulfonic acid at 125°.

EXPERIMENTAL

All melting points were determined on a micro melting point apparatus (Yanagimoto) or in a salt bath, and they are uncorrected. The ir spectra were taken on a Hitachi EPI-S2 spectrophotometer as potassium bromide disks; uv spectra were taken on a Hitachi 220A spectrophotometer in ethanol solution. Mass spectra were recorded on a JEOL JMS-OISG-2 spectrometer. Some physical data, elemental analyses were summarized in table, and the uv spectra of new 2-halobenzofuro[2,3-*c*]quinolines were summarized in Figures 1 and 2.

2-Amino-4-halo-2'-hydroxybenzophenones **7**.

According to the procedure reported by Lamchen and Wichen [3], 2-acetamino-4-halo-2'-methoxybenzophenone **5** was prepared by the Grignard reaction of 6-halo-2-methyl-3,1-benzoxazin-2-ones and (*o*-methoxyphenyl)magnesium bromide in 28% (X = F), 27% (X = Cl), 22% (X = Br), and **5** was purified by recrystallizing from benzene. The hydrolysis of **5** gave the corresponding 2-amino-4-halo-2'-methoxybenzophenones **6** in 91% (X = F), 86% (X = Cl), 93% (X = Br) after refluxing with concentrated hydrochloric acid-ethanol (1:3) for 4 hours, and **6** was purified by recrystallizing from benzene-hexane. Then, **6** was demethylated to the corresponding 2-amino-4-halo-2'-hydroxybenzophenones **7** in 90% (X = F), 79% (X = Cl), 90% (X = Br) after refluxing with 2 equivalents of anhydrous aluminium chloride in dry benzene, and **7** was purified by recrystallization from benzene (X = F, Br) or from ether-hexane (X = Cl).

Condensation of **7** with Chloroacetonitrile to **1** *via* **8**.

According to the procedure reported in our previous paper [1], **7** was condensed with chloroacetonitrile to give the corresponding 2-amino-4-halo-2'-(cyanomethyloxy)benzophenones **8** in 90% (X = F), 95% (X = Cl), 58% (X = Br) after recrystallization from benzene-hexane. This cyanomethoxyl intermediate **8** was cyclized to the corresponding 2-halo-6(5*H*)-benzofuro[2,3-*c*]-quinolinones **1** in 36% (X = F), 31% (X = Cl), 17% (X = Br) by refluxing with potassium hydroxide in 2-ethoxyethanol for 6 hours. These benzofuroquinolinones **1** were effectively purified by recrystallization from 2-ethoxyethanol.

Condensation of **7** with Chloroacetone to **2**.

According to the procedure reported in our previous paper [1], **7** was condensed with chloroacetone to give 2-halo-6-methylbenzofuro[2,3-*c*]quinolines **2** in 72% (X = F), 58% (X = Cl), 54% (X = Br) after refluxing with potassium carbonate in dry acetone for 4 hours. These methylbenzofuroquinolines **2** were purified by recrystallization from benzene-cyclohexane.

Photocyclization of *N*-Benzyl-*N*-(4-halophenyl)-2-benzofurancarboxamides **9** to 2-Halo-5-benzyl-6(5*H*)-benzofuro[2,3-*c*]quinolinones **11**.

According to the procedure reported by Kanaoka and Sannohe [4], photocyclization of the 2-fluoro derivatives **9** (X = F), (501 mg) gave **10** (X = F) (351 mg, 70%) after 70 hours of uv irradiation in acetonitrile (200 ml). This dihydrobenzofuroquinolinone **10** was dehydrogenated to the corresponding **11** (X = F) in 74% after refluxing with 5% palladium-carbon in decaline for 12 hours. But, a similar photocyclization of the 2-chloro derivative **9** (X = Cl) (638 mg) gave a mixture (338 mg, 53% as mixture) of **10** (X = Cl) and **11** (X = Cl) after 80 hours of uv irradiation in acetonitrile (300 ml). This mixture was similarly dehydrogenated to **11** (X = Cl) in 20%. Similar photocyclization of a corresponding bromo derivative **9** (X = Br) (650 mg) gave dehydrogenated **11** (X = Br) only in 68% after 70 hours of uv irradiation in acetonitrile (250 ml).

Debenzylation of **11** to **1**.

According to the procedure reported in our previous paper [1], benzylhalobenzofuroquinolinones **11** (X = F, Cl, Br) was debenzylated to the corresponding 2-halo-6(5*H*)-benzofuro[2,3-*c*]quinolinones **1** in 42% (X = F), 79% (X = Cl), 87% (X = Br) after heating with methanesulfonic acid at 125° for 5 hours.

REFERENCES AND NOTES

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