

Table 1

Some Physical Data and Elemental Analyses of the New Halobenzofuroquinolines **1**, **2**, **8** and **9**

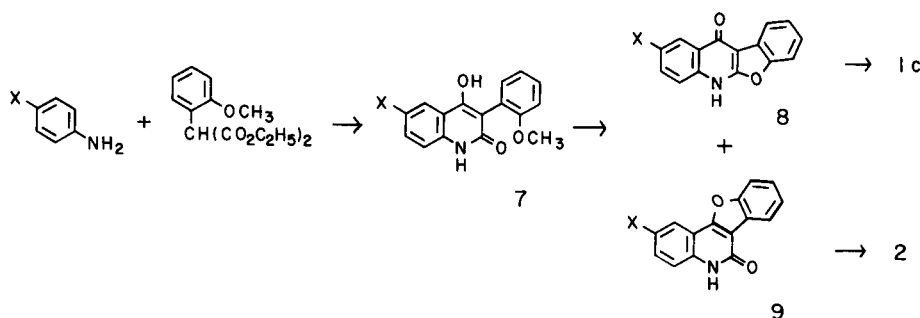
Compound No.	Melting Point (°C)	IR (ν CO) (cm ⁻¹)	Mass (M [*])	Found			Elemental Analyses Empirical Formula	Calcd.		
				C (%)	H (%)	N (%)		C (%)	H (%)	N (%)
1a 8-F	231-232	---	237	76.25	3.44	6.20	C ₁₅ H ₈ FNO	75.94	3.40	5.90
1a 8-Cl	256-257	---	253	71.34	3.31	5.57	C ₁₅ H ₈ ClNO	71.10	3.18	5.52
1a 9-F	225.5-227	---	237	75.91	3.45	6.06	C ₁₅ H ₈ FNO	75.94	3.40	5.90
1a 9-Cl	245-247	---	253	71.21	3.34	5.79	C ₁₅ H ₈ ClNO	71.10	3.18	5.52
1b 9-F	309-311	1705	281	68.46	3.10	5.22	C ₁₆ H ₈ FNO ₃	68.33	2.87	4.98
1c 9-F	195-196	---	271	66.64	2.73	5.37	C ₁₅ H ₇ ClFNO	66.32	2.60	5.16
1c 9-Cl	199-200	---	287	62.76	2.58	5.07	C ₁₅ H ₇ Cl ₂ NO	62.53	2.45	4.86
1c 9-Br	196-197.5	---	331	54.46	2.05	4.24	C ₁₅ H ₇ BrClNO	54.17	2.12	4.21
2 2-F	202-203	---	271	66.35	2.73	4.93	C ₁₅ H ₇ ClFNO	66.32	2.60	5.16
2 2-Cl	226-227	---	287	62.78	2.41	5.06	C ₁₅ H ₇ Cl ₂ NO	62.53	2.45	4.86
2 2-Br	230-231.5	---	331	54.37	2.10	4.18	C ₁₅ H ₇ BrClNO	54.17	2.12	4.21
8 9-F	397-398 dec	1650	253	71.33	3.22	5.81	C ₁₅ H ₈ FNO ₂	71.15	3.18	5.53
8 9-Cl	413-415 dec	1650	269	66.78	3.21	5.30	C ₁₅ H ₈ ClNO ₂	66.81	2.99	5.19
8 9-Br	409-412 dec	1650	313	57.65	2.51	4.54	C ₁₅ H ₈ BrNO ₂	57.35	2.56	4.46
9 2-F	298-300 dec	1660	253	71.33	2.99	5.72	C ₁₅ H ₈ FNO ₂	71.15	3.18	5.53
9 2-Cl	348-350 dec	1670	269	66.77	3.11	5.11	C ₁₅ H ₈ ClNO ₂	66.81	2.99	5.19
9 2-Br	354-356 dec	1680	313	57.30	2.62	4.45	C ₁₅ H ₈ BrNO ₂	57.35	2.56	4.46

Table 2

Some Physical Data and Elemental Analyses of the Intermediate Compounds **4-7**

Compound No.	Melting Point (°C)	IR (cm ⁻¹)	Mass (M [*]) (m/z)	Found			Elemental Analyses Empirical Formula	Calcd.		
				C (%)	H (%)	N (%)		C (%)	H (%)	N (%)
4 6-F	237.5-239	1665	269	71.11	4.43	4.95	C ₁₆ H ₁₂ FNO ₂	71.37	4.49	5.20
4 6-Cl	273-274	1650	285	67.06	4.14	4.68	C ₁₆ H ₁₂ ClNO ₂	67.26	4.23	4.90
4 7-F	202-203.5	1640	269	71.50	4.42	5.00	C ₁₆ H ₁₂ FNO ₂	71.37	4.49	5.20
4 7-Cl	226-227.5	1650	285	67.21	4.16	4.80	C ₁₆ H ₁₂ ClNO ₂	67.26	4.23	4.90
5 2-F	350-351 dec	1730, 1680	281	68.36	2.89	5.00	C ₁₆ H ₈ FNO ₃	68.33	2.86	4.98
5 2-Cl	343-344 dec	1730, 1670	297	64.55	2.75	4.53	C ₁₆ H ₈ ClNO ₃	64.55	2.71	4.71
5 2-Br	348-350 dec	1730, 1670	341	56.42	2.63	4.28	C ₁₆ H ₈ BrNO ₃	56.17	2.36	4.09
5 2-I	377-379 dec	1730, 1655	389	49.11	2.02	3.61	C ₁₆ H ₈ INO ₃	49.38	2.07	3.60
5 3-F	371-373 dec	1720, 1660	281	68.06	2.84	5.03	C ₁₆ H ₈ FNO ₃	68.33	2.86	4.98
5 3-Cl	362-363 dec	1735, 1655	297	64.73	2.63	4.90	C ₁₆ H ₈ ClNO ₃	64.55	2.71	4.71
5 3-Br	374-376 dec	1735, 1655	341	55.94	2.24	4.05	C ₁₆ H ₈ BrNO ₃	56.17	2.36	4.09
5 3-I	377-379 dec	1730, 1655	389	49.33	2.02	3.61	C ₁₆ H ₈ INO ₃	49.38	2.07	3.60
6 2-F	235-236.5	1730	299	64.15	2.60	4.95	C ₁₆ H ₇ ClFNO ₂	64.13	2.35	4.67
6 2-Cl	230-231	1730	315	61.13	2.50	4.71	C ₁₆ H ₇ Cl ₂ NO ₂	60.78	2.23	4.43
6 2-Br	289-290.5	1730	359	53.60	2.08	4.08	C ₁₆ H ₇ BrClNO ₂	53.29	1.96	3.88
6 2-I	292-293	1730	407	47.21	2.00	3.70	C ₁₆ H ₇ ClINO ₂	47.15	1.73	3.44
7 6-F	318-321 dec	1650	285	67.10	4.28	4.99	C ₁₆ H ₁₂ FNO ₃	67.37	4.24	4.91
7 6-Cl	314-316 dec	1650	301	63.43	3.96	4.68	C ₁₆ H ₁₂ ClNO ₃	63.69	4.01	4.64
7 6-Br	306-308 dec	1640	345	55.67	3.67	43.11	C ₁₆ H ₁₂ BrNO ₃	55.51	3.49	4.05

Chart 3



All halo compounds obtained showed similar ir spectra to the corresponding non-halo compounds reported.

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 as potassium bromide disks. Mass spectra were recorded on a JEOL LMS-OISG-2 mass spectrometer. The physical data and elemental analyses are summarized in tables.

Halo-3-(2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-4-carboxylic Acids **3**.

According to the Pfizinger procedure reported in our previous paper [1a], a mixture of 5- or 6-haloanisatin (ca. 15 mmoles), (2-methoxyphenyl)acetic acid (1.75 equivalents), and anhydrous sodium acetate (0.3 g) was heated at 200-230° for 50 minutes. To the hot solution, acetic acid (ca. 20 ml) was added. And, after cooling, the acetic acid solution of the reaction mixture was dissolved in sodium carbonate solution. Acidification of the sodium carbonate solution with hydrochloric acid gave a crude precipitate, which was recrystallized from acetic acid to give pure halo-3-(2-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-4-carboxylic acid **3**. The yields of **3** were the following: 6-F, 49%; 6-Cl, 47%; 6-Br, 35%; 6-I, 26%; 7-F, 58%; 7-Cl, 54%; 7-Br, 81%; 7-I, 81%.

Decarboxylation of **3** to Halo-3-(2-methoxyphenyl)-2(1H)-quinolinone (**4**).

The halocarboxylic acid **3** (ca. 5 mmoles) was dissolved in quinoline (18 ml), and copper powder (1.9 g) was added to the solution. The mixture was refluxed for 8 hours. After cooling, the mixture was dissolved in chloroform. The chloroform layer was washed with 10% hydrochloric acid, saturated sodium carbonate solution, and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. Removal of chloroform gave crude precipitates, which was recrystallized from ethanol to give pure halo-3-(2-methoxyphenyl)-2(1H)-quinolinone **4**. The yields of **4** were the following: 6-F, 46%; 6-Cl, 44%; 7-F, 56%; 7-Cl, 46%. The bromo and iodo derivatives caused dehalogenation and did not give the corresponding decarboxylated compounds.

Demethyl-cyclization of **4** to Halobenzofuro[2,3-*b*]quinolines **1a**.

A mixture of halo-2(1H)-quinolinone **4** (ca. 3 mmoles) and pyridine hydrochloride (10 g) was refluxed for 5 hours. After cooling, the mixture was treated with water, and the precipitates were filtered. The precipitates were recrystallized from ethanol to give pure halo-benzofuro-[2,3-*b*]quinoline **1a**. The yields of **1a** were the following: 8-F, 67%; 8-Cl, 59%; 9-F, 71%; 9-Cl, 89%.

Demethyl-cyclization of **3** to the Lactone **5**.

A mixture of acid **3** (ca. 10 mmoles) and pyridine hydrochloride (30 g) was refluxed for 1 hour, and the cooled reaction mixture was treated with water. The precipitates formed were washed with saturated sodium

hydrogencarbonate solution and collected. Recrystallization of the precipitates gave pure halo-11,12-dihydro-5H-[1]benzopyrano[4,3-*c*]quinolin-5,11-dione **5**. The yields of **5** were the following: 2-F, 54%; 2-Cl, 57%; 2-Br, 44%; 2-I, 56%; 3-F, 82%; 3-F, 82%; 3-Cl, 78%; 3-Br, 84%; 3-I, 46%.

Chlorination of **5** to Chlorolactone **6**.

A mixture of lactone **5** (ca. 4 mmoles), phosphorus pentachloride (2 g), and phosphoryl chloride (10 ml) was vigorously refluxed for 2 hours. The precipitates formed were collected and recrystallized from ethanol to give pure halo-11-chloro-5,11(12H)-benzofuro[4,3-*c*]quinolinedione **6**. The yields of **6** were the following: 2-F, 41%; 2-Cl, 47%; 2-Br, 53%; 2-I, 44%; 3-F, 33%; 3-Cl, 17%; 3-Br, 14%; 3-I, 19%.

Conversion of **10** to Carboxylic Acid **1b**.

A mixture of **6** (ca. 1 mmole), 50% potassium hydroxide aqueous solution (0.5 ml), and dimethyl sulfoxide (10 ml) was refluxed for 6 hours. The cooled reaction mixture was treated with water and filtered. The filtrate was acidified to pH 4 with dilute hydrochloric acid. The white precipitate was collected and recrystallized from ethanol to give pure halobenzofuro[2,3-*b*]quinoline-11-carboxylic acid **1b**. Only one carboxylic acid **1b** (9-F) was obtained in 25%, and in the other instances decarboxylation and hydrolysis occurred.

Condensation of 4-Haloaniline with Diethyl (2-Methoxyphenyl)malonate to 6-Halo-4-hydroxy-3-(2-methoxyphenyl)-2(1H)-quinolinones **7**.

A mixture of 4-haloaniline (ca. 7 mmoles), diethyl (2-methoxyphenyl)malonate, and diphenyl ether (ca. 4 g) was vigorously refluxed for 1 hour. The reaction mixture was extracted with 5% sodium hydroxide solution, and the alkaline solution was acidified with 10% hydrochloric acid. The precipitate was collected and recrystallized from acetic acid to give 6-halo-4-hydroxy-3-(2-methoxyphenyl)-2(1H)-quinolinone **7**. The yields of **7** were the following: F, 71%; Cl, 53%; Br, 68%. The iodo derivative was dehalogenated.

Demethyl-cyclization of **7**.

A mixture of **7** (ca. 5 mmoles) and anhydrous pyridine hydrochloride (15 g) (bp 218°) was vigorously refluxed for 1.5 hours. The cooled reaction mixture was treated with water, and the resulting precipitate was collected. Then the precipitate was treated with a 5% sodium hydroxide aqueous solution and filtered. The remaining precipitate was crystallized from acetic acid to give the pure 2-halo-6(5H)-benzofuro[3,2-*c*]quinolinone **9**. The filtrate was acidified with dilute hydrochloric acid, and the resulting precipitate was collected and recrystallized from pyridine to give pure 9-halo-11(6H)-benzofuro[2,3-*b*]quinolinone **8**. The yields of **8** and **9** were following: F, 64% of **8** and 13% of **9**; Cl, 57% of **8** and 10% of **9**; Br, 66% of **8** and 12% of **9**.

Conversion of **8** or **9** to Chlorohalobenzofuroquinolines **1c** or **2**.

A mixture of **8** or **9** (ca. 2.3 mmoles), phosphorus pentachloride (ca. 3 mmoles), and phosphoryl chloride (6 ml) was refluxed for 2 hours. The cooled reaction mixture was treated with water, and the resulting pre-

cipitate was crystallized from cyclohexane to give pure chlorohalobenzo-furoquinoline **1c** or **2**. The yields of **1c** and **2** were the following: **1c**, F, 59%; Cl, 89%; Br, 89%; **2**, F, 58%; Cl, 50%; Br, 88%.

REFERENCES AND NOTES

- [1a] Y. Kawase, S. Yamaguchi, O. Maeda, A. Hayashi, I. Hayashi, K. Tabata, and M. Kondo, *J. Heterocyclic Chem.*, **16**, 487 (1979); [1b] Y. Kawase, S. Yamaguchi, M. Morita and T. Uesugi, *Bull. Chem. Soc. Japan*, **53**, 1057 (1980); [1c] S. Yamaguchi, Y. Yoshimoto, R. Murai, F. Masuda, M. Yamada and Y. Kawase, *J. Heterocyclic Chem.*, **21**, 737 (1984).