The Synthesis of Benzofuroquinolines. V.
Some Benzofuro[3,2-*b*]quinoline Derivatives

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Some benzofuro[3,2-*b*]quinoline derivatives **1a-d** and **3a** were synthesized by condensation of 2-aminobenzaldehyde, 2-aminoacetophenone, 2-aminobenzophenone, isatin, or 2-aminobenzoic acid with 3(2*H*)-benzofuranone. The benzofuroquinolinone **3a** was also obtained from 2-aminobenzoic acid and phenoxyacetyl chloride in two steps and converted to 10-chloro derivative **1e**. Similarly, some 8-halobenzofuro[3,2-*b*]quinoline derivatives **1d,e** and **3a** (X = F, Cl, Br, I) were synthesized from 5-haloisatin or 2-amino-5-halobenzoic acid. And benzofuro[3,2-*b*]quinolines **1a-e** thus obtained were converted to corresponding *N*-oxides **2**.

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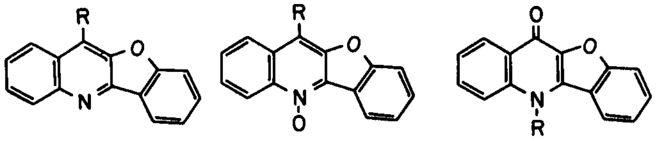
In the course of our studies of polycyclic heteroaromatic compounds, we studied the synthesis of benzofuroquinolines in order to investigate their chemical reactivities and also to test their activities as mutagens, carcinogens, and also antitumor substances. In our previous paper [1], we reported the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

Chart 1



1 a,b,c,d,e 2 a,b,c,d,e 3 a,b

a) R = H b) R = Me c) R = Ph d) R = CO_2H
e) R = Cl

Kempter *et al.* [2] and Bose *et al.* reported the synthesis of 10-methyl- and 10-phenylbenzofuro[3,2-*b*]quinoline (**1b** and **1c**) and benzofuro[3,2-*b*]quinoline-10-carboxylic acid (**1d**) by condensation of 2-aminoacetophenone, 2-aminobenzophenone, and isatin with 3(2*H*)-benzofuranone. Recently, Gorlitzer [4] and Sunder *et al.* [5] reported the synthesis of 10(5*H*)-benzofuro[3,2-*b*]quinoline by condensation of 2-aminobenzoic acid with 3(2*H*)-benzofuranone or phenoxyacetyl chloride and conversion to 10-chlorobenzo-

Chart 2

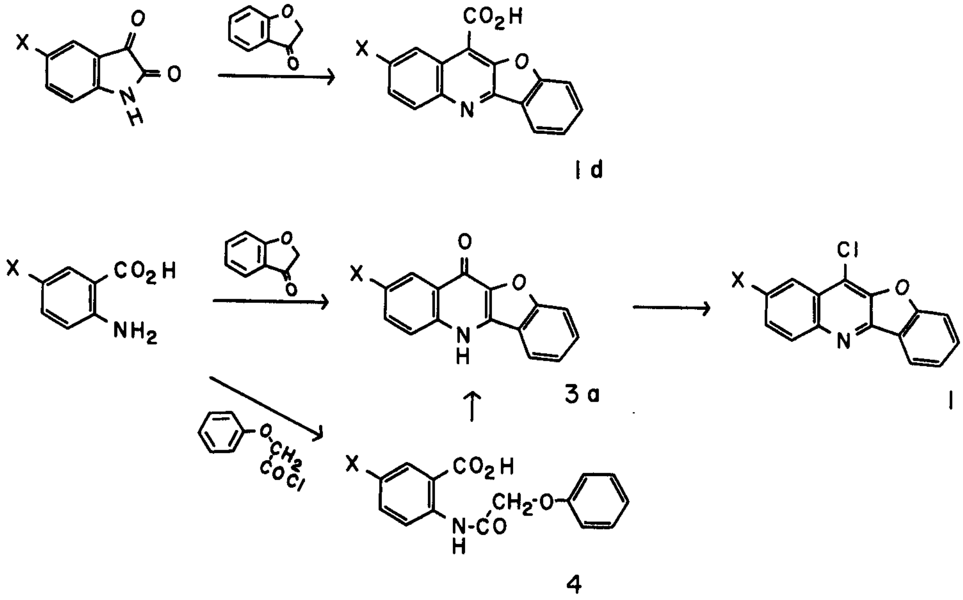


Table 1

The Physical Data and Elemental Analyses of the New Benzofuro[3,2-*b*]quinolines

Compound No.	Melting Point (°C)	IR (cm^{-1})	Mass (M$^+$) (m/z)	Found			Elemental Analyses Empirical Formula	Calcd.		
				C (%)	H (%)	N (%)		C (%)	H (%)	N (%)
1a	156-157	----	219	82.26	4.07	6.35	$C_{15}H_9NO$	82.17	4.14	6.39
2a	212-215	----	235	76.43	3.83	6.25	$C_{15}H_9NO_2$	76.58	3.86	5.96
2b	215-216	----	249	77.03	4.32	5.53	$C_{16}H_{11}NO_2$	77.09	4.45	5.62
2c	239-241	----	311	81.11	4.08	4.26	$C_{21}H_{13}NO_2$	81.01	4.21	4.50
2d	279-280	1690	279	68.76	3.02	5.23	$C_{16}H_9NO_4$	68.82	3.25	5.02
2e	170-172	----	269	67.04	2.78	5.02	$C_{15}H_8ClNO_2$	66.81	2.99	5.19
3b	*ca.* 430 dec	1650	249	76.94	4.45	5.71	$C_{16}H_{11}NO_2$	77.09	4.45	5.62

Table 2

The Physical Data and Elemental Analyses of the Halobenzofuro[3,2-*b*]quinolines

Compound No.		Melting Point (°C)	IR (ν CO) (cm^{-1})	Mass (M$^+$) (m/z)	Found			Elemental Analyses Empirical Formula	Calcd.		
					C (%)	H (%)	N (%)		C (%)	H (%)	N (%)
1d	X = F	301-302 dec	1720	281	68.10	2.91	5.04	$C_{16}H_8FNO_3$	68.33	2.87	4.98
	X = Cl	312-314 dec	1720	297	64.73	2.85	4.44	$C_{16}H_8ClNO_3$	64.55	2.71	4.71
	X = Br	296-298 dec	1730	341	56.34	2.44	4.12	$C_{16}H_8BrNO_3$	56.17	2.36	4.09
	X = I	294-295 dec	1700	389	49.65	2.14	3.46	$C_{16}H_8INO_3$	49.38	2.07	3.60
1e	X = F	185-186	----	271	66.09	2.40	5.37	$C_{15}H_7ClFNO$	66.32	2.60	5.16
	X = Cl	217.5-220.5	----	287	62.23	2.70	5.10	$C_{15}H_7Cl_2NO$	62.52	2.45	4.86
	X = Br	228-229	----	331	54.38	2.03	4.22	$C_{15}H_7BrClNO$	54.17	2.12	4.21
2d	X = F	299-300 dec	1700	297	64.51	2.49	4.48	$C_{16}H_8FNO$	64.65	2.71	4.71
	X = Cl	301-303 dec	1720	313	61.27	2.54	4.56	$C_{16}H_8ClNO_4$	61.26	2.57	4.47
	X = Br	295-296 dec	1710	357	53.50	1.99	3.65	$C_{16}H_8BrNO_4$	53.62	2.25	3.91
2e	X = Cl	228.5-229.5	----	303	59.28	2.41	4.42	$C_{15}H_7Cl_2NO_2$	59.23	2.32	4.61
	X = Br	255-257	----	346	51.84	2.03	4.29	$C_{15}H_7BrClNO_2$	51.68	2.03	4.02
3a	X = F	*ca.* 430	1650	253	70.98	3.31	5.76	$C_{15}H_8FNO_2$	71.15	3.18	5.53
	X = Cl	*ca.* 490	1640	269	66.51	4.97	3.07	$C_{15}H_8ClNO_2$	66.80	5.19	3.00
	X = Br	*ca.* 480	1640	313	57.22	2.53	4.58	$C_{15}H_8BrNO_2$	57.35	2.57	4.46
4	X = F	240-242	1700, 1670	289	62.14	4.20	5.07	$C_{15}H_{12}FNO_4$	62.28	4.19	4.84
	X = Cl	238-239.5	1700, 1670	305	58.79	3.97	4.29	$C_{15}H_{12}ClNO_4$	58.92	3.96	4.58
	X = Br	241-243	1705, 1680	349	51.58	3.66	4.22	$C_{15}H_{12}BrNO_4$	51.44	3.46	4.00
	X = I	250.5-251.5	1700, 1665	377	45.60	3.11	3.80	$C_{15}H_{12}INO_4$	45.36	3.05	3.53

furo[3,2-*b*]quinoline (**1e**). We prepared these compounds **1b-e** by the reported procedure, and benzofuro[3,2-*b*]quinoline (**1a**), having no substituent, from 2-aminobenzaldehyde and 3(2*H*)-benzofuranone by a method reported by Reid [6]. These benzofuro[3,2-*b*]quinoline derivatives **1a-e** were converted to corresponding *N*-oxides **2a-e**. In uv spectra, very interestingly, all benzofuro[3,2-*b*]quinolines **1a-e** showed a similar spectral pattern in spite of the differences of the substituents. It means that the phenyl and carboxyl groups do not affect the conjugation system of benzofuro[3,2-*b*]quinoline ring. But, **3a** showed different spectra in ir and uv, and it means that **3a** has not a benzofuroquinolinol but a benzofuroquinolinone structure. Therefore, **3a** was easily converted to its *N*-methyl derivative by methylation with methyl iodide.

Similarly, four 8-halobenzofuro[3,2-*b*]quinoline-10-carboxylic acids **1d** (X = F, Cl, Br, I) were synthesized from 5-haloisatin and 3(2*H*)-benzofuranone. And three 8-halo-10(5*H*)-benzofuro[3,2-*b*]quinolines **3a** (X = F, Cl, Br) were synthesized from 2-amino-5-halobenzoic acid and 3(2*H*)-benzofuranone or phenoxyacetyl chloride, and converted to 10-chloro-8-halobenzofuro[3,2-*b*]quinolines **1e** (X = F, Cl, Br). But, cyclization of iodoamide **4** (X = I) and condensation of 2-amino-5-iodobenzoic acid caused deiodation and iodobenzofuro[3,2-*b*]quinolinone **3a** (X = I) was not obtained. Some physical data and elemental analyses of these halobenzofuro[3,2-*b*]quinoline derivatives **1d-e, 2d-e, 3a** were summarized in Table 2.

Table 3

UV Spectral Data of Benzofuro[3,2-*b*]quinolines and their *N*-Oxides

Compound No.	λ max (log ε) (nm)
1a	222 sh (4.53), 254 (4.63), 259 (4.73), 327 (4.28), 336 (4.28), 342 (4.25)
1b	227 sh (4.49), 251 sh (4.63), 259 (4.84), 279 (3.53), 309 sh (4.02), 325 (4.32), 335 (4.31), 340 (4.29), 350 sh (4.01)
1c	254 sh (4.60), 260 (4.68), 299 (3.55), 333 (4.27), 340 (4.27)
1d	225 sh (4.42), 253 sh (4.57), 260 (4.64), 308 (3.83), 328 (4.22), 339 (4.22)
1e	230 sh (4.45), 240 sh (4.39), 255 (4.71), 261 (4.79), 280 sh (3.68), 313 sh (4.13), 328 (4.82), 337 (4.32), 345 sh (4.27)
2a	229 (4.34), 272 (4.80), 332 sh (3.96), 346 (4.21), 363 (3.96)
2b	230 (4.32), 273 (4.77), 331 (3.90), 346 (4.17), 366 (3.92)
2c	262 (4.54), 273 (4.55), 335 (4.08), 348 (4.17), 371 (3.79), 392 (3.86)
2d	226 (4.26), 274 (4.71), 333 (3.96), 348 (4.14), 370 (3.95)
2e	240 (4.28), 255 (4.43), 261 (4.46), 280 (3.80), 313 (4.03), 327 (4.09), 437 (4.07), 443 (4.04), 362 sh (3.69)
3a	229 (4.18), 257 (4.60), 265 sh (4.55), 280 sh (3.90), 298 sh (4.14), 310 (4.29), 331 (3.89), 345 (4.21), 362 (4.25)

EXPERIMENTAL

All melting points were determined on a micro melting points apparatus (Yanagimoto) or in a salt bath, and are uncorrected. 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 mass spectrometer. The physical data, elemental analyses, and uv spectral data are summarized in Table 1-3.

Benzofuro[3,2-*b*]quinoline (**1a**).

According to the procedure reported by Ried [6], the preparation of **1a** was effected by the reaction of 2-aminobenzaldehyde with 3(2*H*)-benzofuranone. The crude **1a** was recrystallized from cyclohexane to give pure benzofuro[3,2-*b*]quinoline (**1a**) in 24% yield.

10-Methyl and 10-phenylbenzofuro[3,2-*b*]quinoline (**1b** and **1c**).

According to the procedure of Kempter *et al.* [2], 10-methylbenzofuro[3,2-*b*]quinoline (**1b**) and 10-phenylbenzofuro[3,2-*b*]quinoline (**1c**) were prepared in 41% and 30% yield, respectively.

Benzofuro[3,2-*b*]quinoline-10-carboxylic Acids **1d**.

According to the procedure of Bose *et. al.* [3], benzofuro[3,2-*b*]quinoline-10-carboxylic acid and its 8-halo derivatives **1d** were prepared by condensation of isatin or 8-haloisatins with 3(2*H*)-benzofuranone in 13% (X = H), 12% (X = F), 19% (X = Cl), 20% (X = Br), and 22% (X = I).

10(5*H*)-Benzofuro[3,2-*b*]quinolinones (**3a**).

a) According to the procedure of Gorlitzer [4], 10(5*H*)-benzofuro[3,2-*b*]quinolinones **3a** were prepared by condensation of 2-aminobenzoic acids with 3(2*H*)-benzofuranone in 13% (X = H), 10% (X = F), and 3% (X = Cl). But, its bromo and iodo derivatives were not available by this procedure.

b) According to the procedure of Sunder *et al.* [5], 10(5*H*)-benzofuro[3,2-*b*]quinolinone and its 8-halo derivatives **3a** were also prepared by condensations of 2-aminobenzoic acid or 2-amino-5-halobenzoic acid with phenoxyacetyl chloride in two steps *via* amides **4** in 14% (X = H), 3% (X = F), 4% (X = Cl), and 16% (X = Br). But, cyclization of iodoamide **4** (X = I) caused dehalogenation and iodobenzofuroquinolinone **3a** (X = I) was not available.

10-Chlorobenzofuro[3,2-*b*]quinolines **1e**.

A mixture of benzofuroquinolinones **3a** (*ca.* 4 mmoles), phosphoryl chloride (10 ml), and phosphorus pentachloride (1.0 g) was vigorously refluxed for 2 hours. After cooling, the reaction mixture was treated with water. The precipitates formed were collected and recrystallized from ethanol to give corresponding 10-chlorobenzofuro[3,2-*b*]quinolines in 84% (X = H), 24% (X = F), 68% (X = Cl), and 65% (X = Br).

5-Methyl-10(5*H*)-benzofuro[3,2-*b*]quinolinone **3b**.

A mixture of benzofuroquinolinone **3a** (X = H), methyl iodide (1.0 g), sodium hydroxide (830 mg), and ethanol (20 ml) was refluxed for 3 hours. After cooling, the mixture was treated with water. The precipitates obtained were collected and recrystallized from acetic acid to give 5-methyl-10(5*H*)-benzofuro[3,2-*b*]quinolinone (**3b**) in 27% yield.

N-Oxidations of the Benzofuroquinolines **1a-e**.

To a solution of the benzofuroquinolines **1a-e** (*ca.* 1.0 mmole) in trifluoroacetic acid (2 ml), 30% hydrogen peroxide aqueous solution (0.2 ml) was added, and the mixture was heated at 60-70° for 3 hours. The heating was continued at the same temperature for 6 additional hours with the addition of more 30% hydrogen peroxide aqueous solution (0.2 ml). The reaction mixture was neutralized with saturated sodium carbonate aqueous solution. The precipitates formed were collected and recrystallized from ethanol or acetic acid (**2d**) to give pure *N*-oxides in 38% (**2a**), 37% (**2b**), 62% (**2c**), 76% (**2d**) (X = H), 51% (**2e**) (X = H).

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