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A new and efficient synthesis of benzofuro[3,2-*b*]quinolin-6(11*H*)one (**3**) is reported, by treatment of 2-{[(phenoxy)acetyl]amino}benzoic acid (**6a**) with polyphosphoric acid. An intermediate in the conversion of **3** to **6a**, namely, 2-(3-benzofuranylamino)benzoic acid (**7**), was defined. An improved method for the synthesis of **6a** is also described, which was used to prepare analogs (**6b-n**) of **6a**. In addition, an 11-alkoxy derivative (**8**) and 11-dialkylamino derivatives (**10** and **11**) of benzofuro[3,2-*b*]quinoline were prepared from **3**.

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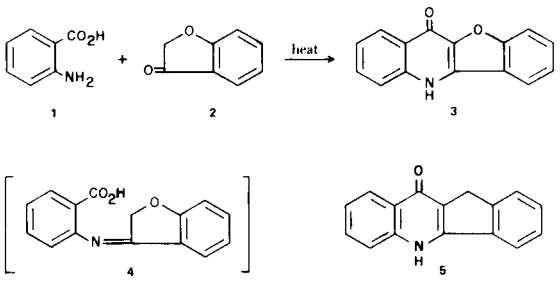
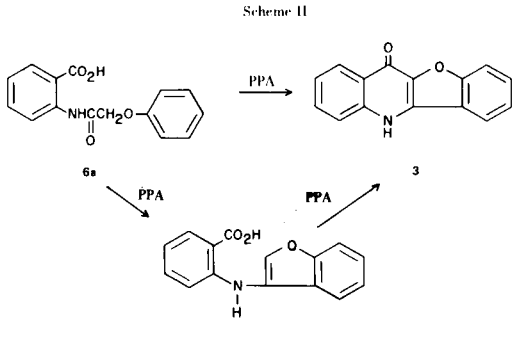
A recent paper by Gorlitzer (1) describes the synthesis of benzofuro[3,2-*b*]quinolin-6(11*H*)one (**3**) from anthranilic acid (**1**) and 3-coumaranone (**2**), as shown in Scheme I. The reaction was done thermally and an 18% yield of **3** was obtained. The author surmised that the thermal condensation proceeded *via* the Schiff base intermediate **4**, since *N*-methylanthranilic acid did not condense with **2** to give any recognizable product. Also, methylene analog **5** could be prepared in similar fashion, from 1-indanone and **1** (2,3).

Scheme I



We have also effected a preparation of benzofuro-[3,2-*b*]quinolin-6(11*H*)one (**3**), using a different approach, which has resulted in a more efficient preparation of this ring system. Treatment of 2-{[(phenoxy)acetyl]amino}-benzoic acid (**6a**) with polyphosphoric acid at elevated temperature gave **3**, in 57% yield after crystallization (Scheme II). Moreover, the identity of an intermediate in

Scheme II



this transformation was determined. In performing the conversion of **6a** to **3** on a larger scale, employing a slightly lower reaction temperature and a shorter reaction time, only a 31% yield of **3** resulted. In addition, we obtained a 40% yield of 2-(3-benzofuranylamino)benzoic acid (**7**). Indeed, we were able to demonstrate that benzofuran **7** was an intermediate in the conversion of **6a** to **3**. Treatment of **7** with polyphosphoric acid at elevated temperature led to a 97% yield of **3**. It can be noted that **7** is a tautomer of intermediate **4**, and, therefore, is coincidentally the same intermediate as proposed by Gorlitzer (1) in his route to **3**. The nmr spectrum of **7**, which was helpful in determining its structure, displayed a singlet at δ 7.64 for the benzofuranyl proton adjacent to oxygen.

Only one literature report describes the synthesis of phenoxyacetamide **6a**. Baker and Hurlbut (5) treated anthranilic acid with phenoxyacetyl chloride in a mixture of dimethylformamide and aqueous sodium hydroxide, and obtained an 18% yield of **6a**. When we used aqueous sodium hydroxide as the sole reaction medium (*i.e.*, the traditional Schotten-Baumann reaction conditions), we obtained a 70% yield of **6a**. In similar fashion, we prepared the series of phenoxyacetamides (**6b-n**) shown in Table I, employing anthranilic acid or 4-chloroanthranilic acid and the appropriately substituted phenoxyacetyl chlorides. Physical constants and yields, which were respectable in most cases, for phenoxyacetamides **6a-n** are listed in Table I.

Scheme III

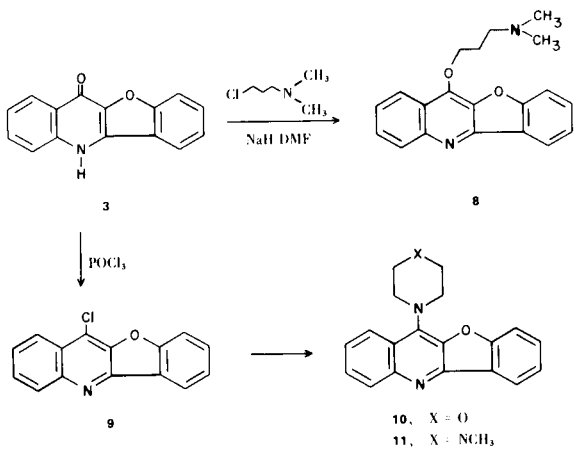
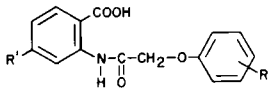


Table I

2-([Phenoxy)acetyl]amino)benxoic Acids



Compound No.	R	R^1	M.p., °C	Recrystallization Solvent	% Yield	Empirical Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
6a	H	H	201-203	Ethanol	70.5	$C_{15}H_{13}NO_4$						
6b	H	Cl	248-250	Ethanol	67.8	$C_{15}H_{12}ClNO_4$	58.92	3.95	4.58	58.62	4.13	4.59
6c	*p*-OCH_3	H	203-205	Ethanol-Ethyl Acetate	53.0	$C_{16}H_{15}NO_5$	63.78	5.02	4.65	63.60	5.15	4.75
6d	*p*-OCH_3	Cl	225-226	Ethanol-Ethyl Acetate	46.5	$C_{16}H_{14}ClNO_5$	57.23	4.20	4.17	57.30	4.34	4.29
6e	*o*-CH_3	H	173-175	Ethanol	53.2	$C_{16}H_{15}NO_4$	67.36	5.30	4.91	67.20	5.33	4.99
6f	*o*-CH_3	Cl	213-214	Ethanol	44.0	$C_{16}H_{14}ClNO_4$	60.09	4.41	4.38	59.80	4.50	4.59
6g	*p*-Cl	H	221-223	Ethanol	34.6	$C_{15}H_{12}ClNO_4$	58.92	3.95	4.58	58.80	3.91	4.78
6h	*p*-Cl	Cl	262-265	Ethanol	48.0	$C_{15}H_{11}Cl_2NO_4$	52.96	3.26	4.11	53.10	3.46	4.39
6i	2,4,5-Cl_3	H	277-278	Ethyl Acetate	49.2	$C_{15}H_{10}Cl_3NO_4$	48.09	2.69	3.74	47.90	2.59	3.90
6j	2,4,5-Cl_3	Cl	288-290	Ethyl Acetate	46.4	$C_{15}H_9Cl_4NO_4$	44.04	2.21	3.42	44.10	2.32	3.69
6k	3,4-Cl_2	H	257-258	Ethanol-Ethyl Acetate	42.2	$C_{15}H_{11}Cl_2NO_4$	52.96	3.26	4.12	53.10	3.29	4.16
6l	3,4-Cl_2	Cl	276-278	Ethanol-Ethyl Acetate	43.6	$C_{15}H_{10}Cl_3NO_4$	48.09	2.69	3.74	47.80	2.75	3.85
6m	3,4-methylene-dioxy	H	219-221	Ethanol-Ethyl Acetate	73.4	$C_{16}H_{13}NO_6$	60.95	4.16	4.44	60.90	4.25	4.40
6n	*p*-CN	H	247-250	Ethyl Acetate	77.8	$C_{16}H_{12}N_2O_4$	64.86	4.08	9.46	64.8	4.20	9.35

Having devised an efficient synthetic route for quinolinone **3**, we elected to prepare some derivatives (Scheme III). Treatment of **3** with 3-(dimethylamino)propyl chloride and sodium hydride in dimethylformamide gave 3-[benzofuro[3,2-*b*]quinolin-6-yloxy]-*N*,*N*-dimethyl-1-propanamine (**8**). Another mode of derivatization involved the treatment of **3** with phosphorus oxychloride to yield 11-chlorobenzofuro[3,2-*b*]quinoline (**9**). Displacement reactions of **9** with morpholine and *N*-methylpiperazine yielded the 11-substituted derivatives **10** and **11**, respectively.

The improved method reported here for the preparation of **3** should make the benzofuro[3,2-*b*]quinoline ring system more accessible. The phenoxyacetamides listed in Table I, also prepared using an improved procedure, were easily accessible and demonstrate the potential for preparing a variety of substituted analogs of **3**.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727 Spectrophotometer, nmr spectra with a Varian T-60 spectrometer, and mass spectra with a Finnigan gc/ms Model 3000D (electron impact and chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories.

Materials.

Anthranilic acid (**1**), 4-chloro-2-aminobenzoic acid and phenoxyacetyl chloride were obtained commercially (Aldrich). *p*-Methoxyphenoxyacetyl chloride, b.p. 118° (1.5 mm), [lit. (6) b.p. 159-160° (20 mm)]; *o*-methylphenoxyacetyl chloride, b.p. 87° (0.7 mm), [lit. (7) b.p. 120° (10 mm)]; *p*-chlorophenoxyacetyl chloride, b.p. 130° (10 mm), [lit. (8) b.p. 142° (17 mm)]; 2,4,5-trichlorophenoxyacetyl chloride, m.p. 64-69°, [lit. (9) m.p. 78-79°, b.p. 165-167° (6 mm)]; 3,4-dichlorophenoxyacetyl chloride, b.p. 117-122° (0.1 mm), [lit. (10,11)]; 3,4-methylenedioxyphenoxyacetyl chloride, m.p. 68-70°, [lit. (12) b.p. 103-104° (0.085 mm)]; and *p*-cyanophenoxyacetyl chloride, m.p. 70-73° (13), were prepared using excess thionyl chloride and the appropriate phenoxyacetic acid.

General Method for the Preparation of Phenoxyacetamides (**6a-n**).

Compounds **6a-n** were prepared by treating anthranilic acid or 2-amino-4-chlorobenzoic acid in aqueous sodium hydroxide (two equivalents) with the appropriate phenoxyacetyl chlorides. After the addition, which was done dropwise with icebath cooling, the solution was acidified with dilute hydrochloric acid and the resulting mixture was either filtered or extracted with ethyl acetate to remove the phenoxyacetamide. Purification was accomplished by recrystallization, using the solvent(s) specified in Table I.

Benzofuro[3,2-*b*]quinolin-6(11*H*)one (**3**).

A 5.00 g. (18.4 mmoles) quantity of **6a** and 50 g. of polyphosphoric acid were heated with stirring at 120-130° for 1.5 hours. The solution was treated with crushed ice, basified with sodium carbonate and the resulting solid was collected, washed with water and air-dried to yield 3.7 g. of crude **3**. Recrystallization from dimethyl sulfoxide-water afforded 2.46 g. (57%) of **3**, m.p. > 335°; ir (potassium bromide): 3300-2500 (broad), 1640 (C=O); nmr (trifluoroacetic acid): δ 12.80 (broad s, 1H, NH/OH), 8.57 (d, J = 8 Hz, 1H, aromatic), 8.37-7.33 (m, 7H, aromatic); uv (dioxane): λ max 256, 263, 289, 301, 342, 358; ms (70 eV, chemical ionization, methane): m/e 236 (M^+ + 1), 264 (M^+ + 29), 276 (M^+ + 41); ms (70 eV, electron impact): m/e (relative intensity) 235 (100), 207 (27), 179 (65), 151 (66), 76 (100).

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 76.15; H, 3.86; N, 5.96. Found: C, 76.40; H, 4.00; N, 5.87.

Isolation of 2-(3-Benzofuranylamino)benzoic Acid (**7**).

A 36.5 g. (0.134 mole) quantity of **6a** and 400 g. of polyphosphoric acid were heated with stirring for 1 hour. The solution was treated with crushed ice, basified with sodium carbonate, and the resulting solid was collected, washed with water and air-dried to yield 34 g. of crude yellow solid. Tlc (silica gel; 9:1 chloroform:methanol) of this solid indicated a mixture of two compounds, one of which was **3**. Recrystallization of the solid from 400 ml. of hot dimethylsulfoxide afforded 9.87 g. (31%) of **3**, m.p. > 335°. The filtrate, when diluted with water, produced a precipitate which was collected and air-dried to yield 13.7 g. (40%) of **7**, m.p. 194-196° (chloroform); ir (Nujol): 3350-2400 (broad), 1655 (C=O), 1600 (C=C); nmr (deuteriochloroform plus DMSO-d_6): δ 9.47 (broad s, 1H, NH, deuterium oxide exchangeable), 8.10-7.87 (m, 1H, aromatic), 7.64 (s, 1H, benzofuranyl H adjacent to oxygen), 7.55-7.07 (m, 5H, aromatic), 7.07-6.52 (m, 2H, aromatic); ms (70 eV, chemical ionization, methane): m/e 254 (M^+ + 1), 282 (M^+ + 29), 294 (M^+ + 41).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.40; H, 4.48; N, 5.56.

A 6.40 g. (25.3 mmoles) quantity of **7** and 80 g. of polyphosphoric acid were heated with stirring at 130-140° for 1.5 hours. The solution was treated with crushed ice and neutralized with sodium bicarbonate. The resulting white solid was collected and air-dried to yield 5.80 g. (97%) of crude **3**. This material was recrystallized (dimethyl sulfoxide-water) and was identical in all respects with a sample of **3** prepared directly from **6a**.

3-[Benzofuro[3,2-*b*]quinolin-6-yloxy]-*N*,*N*-dimethyl-1-propanamine (**8**).

To a stirring mixture of 0.550 g. (22.4 mmoles) of dry sodium hydride in 20 ml. of dimethylformamide under a nitrogen atmosphere was added 4.70 g. (20.0 mmoles) of **3**. After 10 minutes, an excess of 3-dimethylaminopropyl chloride (14) was added. The solution was heated at reflux for 5 hours and poured into water. The mixture was extracted with methylene chloride, and the organic layer was dried (sodium sulfate) and concentrated to yield 3.80 g. (59%) of crude **8**, m.p. 104-105° (benzene-hexane); ir (Nujol): 1635 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 8.43-8.06 (m, 3H, aromatic), 7.80-7.20 (m, 5H, aromatic), 4.98 (t, J = 6 Hz, 2H, OCH_2), 2.80-1.88 [m, 10H, $CH_2CH_2N(CH_3)_2$, with dimethylamino singlet at 2.28]; ms (70 eV, chemical ionization, methane): m/e 321 (M^+ + 1), 249 (M^+ + 29), 361 (M^+ + 41).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 75.00; H, 6.38; N, 8.76.

11-Chlorobenzofuro[3,2-*b*]quinoline (**9**).

A 12.9 g. (54.8 mmoles) quantity of **3** was heated at reflux in excess phosphorus oxychloride for 2 hours. The solution was cooled and thoroughly concentrated. The residue was partitioned between methylene chloride and 10% sodium hydroxide, and the dried (sodium sulfate) organic layer was concentrated. Recrystallization of the solid residue from ethanol afforded 11.5 g. (83%) of **9**, m.p. 159-160°; ir (Nujol): 1640, 1595, 1555, 1190, 1135 cm^{-1}; nmr (deuteriochloroform): δ 8.57-8.18 (m, 3H, aromatic), 8.08-7.34 (m, 5H, aromatic).

Anal. Calcd. for $C_{15}H_8ClNO$: C, 71.01; H, 3.18; N, 5.52. Found: C, 71.20; H, 3.24; N, 5.52.

11-(4-Morpholinyl)benzofuro[3,2-*b*]quinoline (**10**).

A 3.00 g. (11.8 mmoles) quantity of **9** in 25 ml. of morpholine was heated at reflux for 18 hours. The concentrated solution was partitioned between methylene chloride and water and the dried (sodium sulfate) organic layer was concentrated to yield 3.53 g. (98%) of **10**, m.p. 180-182° (ethanol); ir (Nujol): 1635, 1600, 1595, 1100, 765, 745 cm^{-1}; nmr (deuteriochloroform): δ 8.57-8.10 (m, 3H, aromatic), 7.97-7.27 (m, 5H, aromatic), 4.30-3.92 (m, 4H, CH_2OCH_2), 3.92-3.47 (m, 4H, CH_2NCH_2).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.70; H, 5.37; N, 9.14.

11-(4-Methyl-1-piperazinyl)benzofuro[3,2-*b*]quinoline (**11**).

A 2.53 g. (98.5 mmoles) quantity of **9** in 25 ml. of 4-methylpiperazine was heated at reflux for 24 hours. The concentrated solution was partitioned between methylene chloride and water and the dried (sodium sulfate) organic layer was concentrated to yield 2.40 g. (77%) of **11**, m.p. 185-186° (ethanol); ir (Nujol): 1630, 1595, 1570, 1180, 1130 cm^{-1}; nmr (deuteriochloroform): δ 8.64-8.17 (m, 3H, aromatic), 7.90-7.27 (m, 5H, aromatic), 3.90-3.50 (m, 4H, 2 CH_2 groups), 2.93-2.45 (m, 4H, 2 CH_2 groups), 2.47 (s, 3H, NCH_3).

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.42; H, 6.12; N, 13.27.

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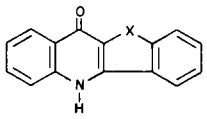
(3) Interestingly, quinolinones i (1) and ii (4), the sulfur and nitrogen analogs of **3**, respectively, have both been prepared using routes dissimilar to those used for **3** and **5**.



i, x = S
ii, x = NH

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(13) *Anal.* Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.34; H, 3.21; N, 7.34.

(14) 3-Dimethylaminopropyl chloride hydrochloride was treated with ether and 50% sodium hydroxide. The decanted ether layer was dried (sodium sulfate) and concentrated to yield the free base.