Synthesis of 11-Aza-5*H*-benzophenoxazin-5-one and 11-Aza-5*H*-pyridophenoxazin-5-one Derivatives

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The 1,6-disubstituted- and 4,6-disubstituted-11-aza-5*H*-benzo[*a*]phenoxazin-5-one as well as 6-substituted-11-aza-5*H*-pyrido[*a*]phenoxazin-5-one derivatives were prepared by the condensation of 2-amino-3-hydroxypyridine with 5-substituted-2,3-dihalogeno-1,4-naphthoquinones and 6,7-dibromo-5,8-quinolinequinone respectively. The resulting compounds were subjected to reduction, acetylation, dehalogenation and reaction with aniline.

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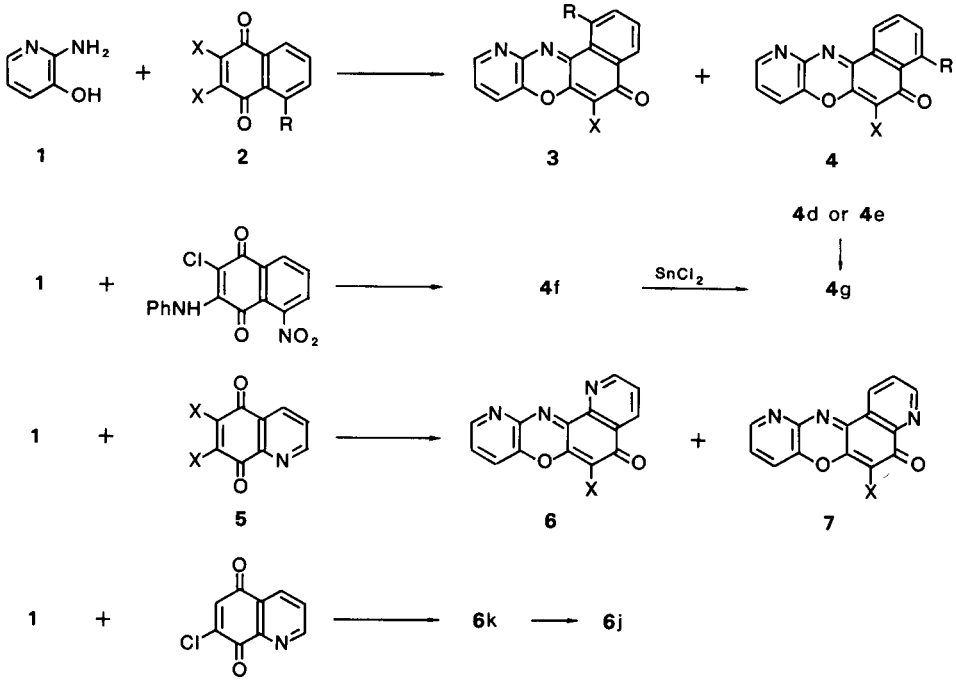
Our interest in the chemistry of phenoxazone and phenothiazone derivatives led us to synthesize the related compounds [1-5]. In this work, 1,6-disubstituted-11-aza-5*H*-benzo[*a*]phenoxazin-5-one **3a-i** and 4,6-disubstituted-11-aza-5*H*-benzo[*a*]phenoxazin-5-one **4a-i** as well as 6-substituted-11-aza-5*H*-pyrido[2,3-*a*]phenoxazin-5-one **6j,k** and 11-aza-6-bromo-5*H*-pyrido[3,2-*a*]phenoxazin-5-one **7j** were prepared by the condensation of 2-amino-3-hydroxypyridine (**1**) with 5-substituted-2,3-dihalogeno-1,4-naphthoquinones (**2**) as well as 6,7-dibromo-5,8-quinolinequinone (**5**) respectively. The condensation of **1** with **2a-c,h** proceeded in benzene-ethanol at room temperature in the presence of potassium acetate, giving **3a-c,h** and **4a-c** in good yields. The compounds **3b** and **4b** were also prepared by the reduction of **3a** and **4a** with stannous chloride in acetic acid in good yields respectively. The dehalogenation of the compounds **3b,c,h** and **4b,c** in the presence of sodium hydrosulfite dissolved in aqueous pyridine under nitrogen atmosphere gave **3d,e,i** and **4d,e** respectively.

Treating **4d** or **4e** with hydrochloric acid and aniline in dimethyl sulfoxide **4g** was produced and identified by

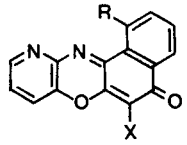


	a	b	c	d	e	f	g	h	i	j	k
R	NO_2	NH_2	NHAc	NH_2	NHAc	NO_2	NH_2	H	H	–	–
X	Cl	Cl	Cl	H	H	NHPh	NHPh	Br	H	Br	H

Scheme I

Table 1

Physical and Analytical Data for Compounds **3**, **4**, **6** and **7**



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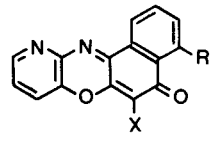

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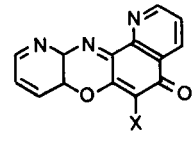

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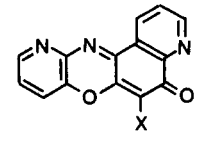

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Compound	R	X	Mp (°C) (recrystallized)	Molecular Formula	Mass (M⁺) (relative intensity %)	Elemental Analyses (%) Found/(Calcd.) C	H	N	Br
3a	NO_2	Cl	397.5-399.0 (Acetone-Chloroform)	$C_{15}H_6ClN_3O_4$ (327.7)	327/329 (100) (44)	55.13 (54.98)	1.60 (1.85)	12.77 (12.82)	
4a	NO_2	Cl	337.0-337.8 (Acetone-Chloroform)	$C_{15}H_6ClN_3O_4$ (327.7)	327/329 (100) (40)	54.71 (54.98)	1.65 (1.85)	13.08 (12.82)	
3b	NH_2	Cl	390.0-392.0 (Benzene)	$C_{15}H_8ClN_3O_2$ (297.7)	297/299 (100) (36)	60.47 (60.52)	2.46 (2.71)	13.79 (14.12)	
4b	NH_2	Cl	345.5-347.5 (Benzene)	$C_{15}H_8ClN_3O_2$ (297.7)	297/299 (100) (37)	60.38 (60.52)	2.60 (2.71)	14.20 (14.12)	
3c	NHAc	Cl	331.5-333.0 (Benzene)	$C_{17}H_{10}ClN_3O_3$ (339.7)	339/341/297/299 (40) (15) (100) (37)	60.21 (60.10)	2.74 (2.97)	12.24 (12.37)	
4c	NHAc	Cl	394.5-397.0 (Benzene)	$C_{17}H_{10}ClN_3O_3$ (339.7)	339/341/297/299 (33) (10) (100) (39)	59.92 (60.10)	2.75 (2.97)	12.27 (12.37)	
3d	NH_2	H	355.5-358.0 (Benzene-Ethyl acetate)	$C_{15}H_9N_3O_2$ (263.3)	263 (100)	68.25 (68.44)	3.09 (3.45)	16.04 (15.96)	
4d	NH_2	H	295.0-297.5 (Benzene-Ethyl acetate)	$C_{15}H_9N_3O_2$ (263.3)	263 (100)	68.57 (68.44)	3.19 (3.45)	15.60 (15.96)	
3e	NHAc	H	279.0-280.0 (Benzene-Ethyl acetate)	$C_{17}H_{11}N_3O_3$ (305.3)	305/263 (39) (100)	66.73 (66.88)	3.29 (3.63)	13.37 (13.76)	
4e	NHAc	H	319.0-320.5 (Benzene-Ethyl acetate)	$C_{17}H_{11}N_3O_3$ (305.3)	305/263 (40) (100)	66.68 (66.88)	3.23 (3.63)	13.70 (13.76)	
4g	NH_2	NHPh	289.0-290.5 (Acetone-Ethanol)	$C_{21}H_{14}N_4O_2$ (354.4)	354 (100)	70.91 (71.18)	3.94 (3.98)	15.60 (15.81)	
3h	H	Br	255.5-257.0 (Benzene)	$C_{15}H_7BrN_2O_2$ (327.1)	326/328 (100) (100)	55.03 (55.07)	2.07 (2.16)	8.63 (8.33)	
3i	H	H	254.0-255.0 (Benzene)	$C_{15}H_8N_2O_2$ (248.2)	248 (100)	72.63 (72.58)	3.11 (3.25)	11.15 (11.28)	
6j	—	Br	296.5-298.0 (Acetone)	$C_{14}H_6BrN_3O_2$ (328.1)	327/329 (94) (100)	51.50 (51.25)	1.83 (1.84)	12.51 (12.81)	24.25 (24.35)
7j	—	Br	283.5-285.0 (Acetone)	$C_{14}H_6BrN_3O_2$ (328.1)	327/329 (89) (100)	51.34 (51.25)	1.64 (1.84)	12.52 (12.81)	24.08 (24.35)
6k	—	H	230.0-233.0 (Acetone)	$C_{14}H_7N_3O_2$ (249.2)	249 (100)	67.75 (67.47)	3.11 (2.83)	16.52 (16.86)	

comparing its ir, uv and ms spectra as well as mixed melting point with the authentic sample which was prepared by the condensation of 3-anilino-2-chloro-5-nitro-1,4-naphthoquinone with **1** followed by the reduction with stannous chloride in acetic acid.

The reaction between **1** and **5** produced **6j** and **7j** under a similar manner to that described above **1** with **2** in moderate yields. The debromination of **6j** and **7j** did not occur under the same condition on **3b,c,h** and **4b,c**.

The structure of **6j** was identified by comparing its ir, uv, nmr, ms spectra and mixed melting point with the authentic sample which was prepared by the condensation of **1** with 7-chloro-5,8-quinolinequinone followed by bromination with bromine in acetic acid.

On the above identifications and the spectroscopic data as well as elemental analyses, the structures of **3**, **4**, **6** and **7** were determined as in Scheme I. The physical and analytical data for the compounds obtained in these reactions are listed in Table 1.

EXPERIMENTAL

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets and the ultraviolet spectra were recorded with a JASCO UVIDEC-505. The nuclear magnetic resonance spectra were measured on a Varian XL-200 spectrometer using tetramethylsilane as the internal standard. Some of the compounds were recorded for 0.5% w/v solutions operating in an FT mode. The mass spectra were obtained with a Hitachi M-52 or ESCO

EMD-05B spectrometer. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh ASTM and Mallinckrodt, 100 mesh) and aluminium oxide (90, Merck, 70-230 mesh ASTM and activated 300, Nakarai Chemicals, Ltd.) were used. One of the starting materials, 2-amino-3-hydroxypyridine was purchased from Aldrich Chemical Company, Inc..

Condensation of 2,3-Dichloro-5-nitro-1,4-naphthoquinone (**2a**) with 2-Amino-3-hydroxypyridine (**1**).

To a stirred suspension of 815 mg (3 mmoles) of **2a** [6] and 0.6 g potassium acetate in 50 ml of benzene-ethanol was added dropwise a solution of 330 mg (3 mmoles) of **1** in 20 ml of ethanol over 25 minutes. After stirring at room temperature for additional 40 minutes, the mixture was concentrated *in vacuo* and washed with water. The residue was column chromatographed on silica gel (Merck, Kieselgel 60) using benzene-ethyl acetate (20:1) as the eluent. From the first orange-yellow fraction 450 mg of 11-aza-6-chloro-1-nitro-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**3a**) and from the second orange fraction 320 mg of 11-aza-6-chloro-4-nitro-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4a**) were obtained. The total yield of the products was 78% in the ratio of 1.4:1.0 (**3a:4a**).

Compound **3a**.

This compound had ir: 1640 (C=O), 1540 and 1368 (NO_2) cm^{-1}; uv (chloroform): λ max, nm (log ε), 457 (4.16), 336 (4.12), 309 sh (4.08), 297 (4.08), 259 (4.25), 246 (4.36); ^1H nmr (deuteriochloroform): δ 8.75 (d, 1H), 8.63 (d, 1H), 8.02-7.83 (m, 3H), 7.57 (m, 1H).

Compound **4a**.

This compound had ir: 1638 (C=O), 1525 and 1378 (NO_2) cm^{-1}; uv (chloroform): λ max, nm (log ε), 457 (4.18), 342 (4.05), 309 sh, 295 (4.01), 259 (4.24), 245 (4.35); ^1H nmr (deuteriochloroform): δ 9.16 (d, 1H), 8.77 (d, 1H), 8.04-7.80 (m, 3H), 7.62 (m, 1H).

Condensation of 5-Amino-2,3-dichloro-1,4-naphthoquinone (**2b**) with **1**.

To a stirred suspension of 484 mg (2 mmoles) of **2b** [6] and 2 ml of 15% hydrochloric acid in 30 ml ethanol was added dropwise a solution of 220 mg (2 mmoles) of **1** in 20 ml of ethanol over 20 minutes. After refluxing for 2 hours, the mixture was concentrated *in vacuo* and washed with water. The residue was chromatographed on Kieselgel 60 using benzene-ethyl acetate (10:1, 2:1) as the eluent. From the first purple fraction 97 mg of 4-amino-11-aza-6-chloro-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4b**) and from the second purple fraction (benzene-ethyl acetate 2:1) 260 mg of 1-amino-11-aza-6-chloro-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**3b**) were obtained. The yield of the products was 60% in the ratio of 2.7:1.0 (**3b:4b**).

Compound **3b**.

This compound had ir: 3305 (NH), 1603 (C=O) cm^{-1}; uv (chloroform): λ max, nm (log ε), 524 (4.03), 430 (4.09), 375 sh (3.97), 357 (4.00), 266 (4.11); ^1H nmr [10].

Compound **4b**.

This compound had ir: 3425 and 3310 (NH), 1607 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 538 (4.07), 446 (3.85), 421 (3.93), 402 sh (3.90), 356 (4.12), 296 (4.01), 264 (4.14); ^1H nmr [10].

Reduction of **3a** and **4a**.

A solution of 5 mmoles of stannous chloride in 8 ml of hydrochloric acid was added to a stirred suspension of 1 mmole of **3a** in 15 ml of acetic acid at room temperature over 10 minutes. After stirring for 30 minutes at 50°, the mixture was filtered. The resulting solid was treated with a solution of ferric chloride in water, giving dark blue crystals in the yield of 85%. This is identical with **3b** which was prepared from **2b** and **1**.

Compound **4a** was similarly reduced to **4b** in 80% yield.

Condensation of 5-Acetylamino-2,3-dichloro-1,4-naphthoquinone (**2c**) with **1**.

Compound **2c** [6] was treated with **1** in the similar manner as the condensation of **2a** with **1**. From the first orange fraction 1-acetylamino-11-aza-6-chloro-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**3c**) and from the second red fraction 4-acetylamino-11-aza-6-chloro-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4c**) were obtained in the yield of 68% in the ratio of 1.0:1.7 (**3c:4c**).

Compound **3c**.

This compound had ir: 1705 and 1642 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 485 sh, 456 (4.15), 370 sh (3.97), 354 (4.01), 267 (4.16); ^1H nmr [10].

Compound **4c**.

This compound had ir: 1678 and 1618 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 485 (4.16), 353 (4.01), 297 sh (3.96), 285 sh (3.99), 265 (4.10); ^1H nmr [10].

Acetylation of **3b**.

The mixture of 0.1 mmole of **3b**, 3 ml of acetic acid and 3 ml of acetic anhydride was refluxed for 15 minutes, giving orange crystals which were identical with **3c** obtained above from **2c** and **1**.

Dechlorination of **3b**, **4b**, **3c** and **4c**.

Treating **3b**, **4b**, **3c** or **4c** with sodium hydrosulfite and pyridine by the similar manner of the preparation of 5*H*-pyrido[*a*]phenoxazin-5-ones [2], chlorine atom in 6-position was substituted by hydrogen atom.

From **3b**, 1-amino-11-aza-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**3d**) was prepared in the yield of 89% (refluxed for 6 hours).

Compound **3d**.

This compound had ir: 3325 (NH), 1600 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 517 (3.99), 415 (4.09), 368 (3.97), 354 (3.96), 263 sh (4.06); ^1H nmr [10].

From **4b**, 4-amino-11-aza-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4d**) was obtained in the yield of 78% (refluxed for 30 minutes).

Compound **4d**.

This compound had ir: 3430 and 3315 (NH), 1605 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 525 (4.03), 437 sh (3.86), 410 (3.98), 392 sh (3.97), 354 (4.09), 295 (4.01), 260 sh (4.15); ^1H nmr (dimethyl sulfoxide-d_6): 50° δ 8.53 (d, 1H), 7.95 (d, 1H), 7.85 (d, 1H), 7.72-7.50 (m, 4H), 7.17 (d, 1H), 6.25 (s, 1H, iminoquinone H).

From **3c**, 1-acetylamino-11-aza-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**3e**) was obtained in the yield of 28% (refluxed for 3 hours).

Compound **3e**.

This compound had ir: 1685 and 1647 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 437 (4.25), 365 sh (4.07), 352 (4.08), 285 sh, 262 (4.28); ^1H nmr (dimethyl sulfoxide-d_6): 80° δ 13.45 (s, 1H, CONH), 9.03 (d, 1H), 8.63 (d, 1H), 7.98-7.80 (m, 3H), 7.64 (m, 1H), 6.49 (s, 1H, iminoquinone H), 2.29 (s, 3H, $COCH_3$).

From **4c**, 4-acetylamino-11-aza-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4e**) was obtained in the yield of 91% (refluxed for 30 minutes).

Compound **4e**.

This compound had ir: 1675 and 1638 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 472 (4.23), 352 (4.06), 292 (4.09), 265 (4.24); ^1H nmr (dimethyl sulfoxide-d_6): 80° δ 12.35 (s, 1H, CONH), 8.95 (m, 1H), 8.64-8.48 (m, 2H), 7.88 (m, 2H), 7.55 (m, 1H), 6.45 (s, 1H, iminoquinone H), 2.18 (s, 3H, $COCH_3$).

Synthesis of 4-amino-6-anilino-11-aza-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4g**).

Route A.

3-Anilino-2-chloro-5-nitro-1,4-naphthoquinone [6] (0.5 mmole) was condensed with **1** (0.5 mmole) in pyridine (20 ml) in the presence of potassium acetate under refluxing for 3 hours. After extracting the mixture with benzene, the resulting benzene layer was chromatographed on Kieselgel 60 column using benzene-ethyl acetate (20:1 and 4:1) as the

eluent. From benzene-ethyl acetate (4:1), 6-anilino-11-aza-4-nitro-5*H*-benzo[6,5-*a*]phenoxazin-5-one (**4f**) was prepared in the yield of 50%. The reduction of **4f** in acetic acid with stannous chloride in hydrochloric acid at 50° for 15 minutes produced yellow mixture, giving **4g** by the treatment with 10% sodium hydroxide solution followed by the column chromatography.

Compound **4f**.

This compound had mp 282-284°; ir: 1635 (C=O), 1543 and 1375 (NO_2), cm^{-1}; uv (chloroform): λ max, nm, 597, 382, 300 sh, 260; ms: m/e 384 (M^+, base peak).

Compound **4g**.

This compound had ir: 3420 and 3300 (NH), 1612 (C=O), cm^{-1}; uv (chloroform): λ max, nm (log ε), 588 (3.97), 482 (3.92), 308 sh (4.18), 288 (4.20); ^1H nmr (dimethyl sulfoxide-d_6): δ 8.37 (m, 1H), 8.02 (s, 1H), 7.94 (d, 1H), 7.88-7.70 (m, 1H), 7.65-7.50 (m, 2H), 7.37-6.89 (m, 8H).

Route B.

To a stirred suspension of **4d** (0.1 mmole) in dimethyl sulfoxide (8 ml) and hydrochloric acid (1 ml) was added 1.5 ml of aniline and stirred for 20 minutes at 110°. After neutralization of the mixture with a sodium hydroxide solution, the product was extracted with benzene and concentrated *in vacuo*. The residue was repeatedly chromatographed on silica gel column (Mallinckrodt 100 mesh) using benzene-ethyl acetate (20:1-1:1) as the eluent giving dark blue crystals which were identical with **4g** in 20% yield.

From **4e** and aniline by the similar treatment described above heating for 2 hours **4g** was also obtained.

Condensation of 2,3-Dibromo-1,4-naphthoquinone (**2h**) with **1**.

The reaction of **2h** [7] and **1** produced 11-aza-6-bromo-5*H*-benzo[*a*]-phenoxazin-5-one (**3h**) by the same way as the condensation of **2a** and **1** in the yield of 70%.

Compound **3h**.

This compound had ir: 1635 (C=O), cm^{-1}: uv (methanol): λ max, nm (log ε), 442 (4.10), 350 (4.09), 263 (4.14), 256 (4.15), 242 (4.26), 234 (4.30); ^1H nmr (deuteriochloroform): δ 8.91 (d, 1H), 8.70 (bs, 1H), 8.39 (d, 1H), 7.86 (m, 3H), 7.58 (bs, 1H).

Debromination of **3h**.

By the same procedure as the dechlorination of **3b**, **3h** afforded 11-aza-5*H*-benzo[*a*]phenoxazin-5-one (**3i**) in the yield of 92%.

Compound **3i**.

This compound had ir: 1638 (C=O), cm^{-1}; uv (methanol): λ max, nm (log ε), 424 (4.16), 345 (4.05), 256 (4.25), 239 (4.13), 232 (4.15); ^1H nmr (deuteriochloroform): δ 8.92 (s, 1H), 8.67 (bs, 1H), 8.32 (m, 1H), 7.85 (m, 2H), 7.72 (d, 1H), 7.52 (bs, 1H), 6.53 (s, 1H, iminoquinone H).

Condensation of 6,7-Dibromo-5,8-quinolinequinone (**5j**) with **1**.

Compound **5j** [8] reacted with **1** by the similar manner as the condensation of **2a** and **1** giving 11-aza-6-bromo-5*H*-pyrido[2,3-*a*]phenoxazin-5-one (**6j**) and 11-aza-6-bromo-5*H*-pyrido[3,2-*a*]phenoxazin-5-one (**7j**) in the yield of 26% in the approximately same ratio. Using aluminium oxide for column chromatography **7j** was obtained from the first fraction and **6j** from the second.

Compound **6j**.

This compound had ir: 1640 (C=O), cm^{-1}; uv (methanol): λ max, nm (log ε), 447 (4.07), 336 (4.05), 291 sh, 282 (4.08), 241 (4.37); ^1H nmr (deuteriochloroform): δ 9.25 (bs, 1H), 8.75 (bs, 2H), 7.85 (m, 2H), 7.62 (m, 1H).

Compound **7j**.

This compound had ir: 1645 (C=O), cm^{-1}; uv (methanol): λ max, nm (log ε), 443, (3.97), 337 (3.92), 283 (3.91), 243 (4.25); ^1H nmr (deuteriochloroform): δ 9.28 (bs, 2H), 8.78 (bs, 1H), 7.96 (d, 1H), 7.87 (m, 1H), 7.66 (m, 1H).

Debromination of **6j** and **7j** did not occur under the same conditions as the dechlorination of **3b** *etc.*, with sodium hydrosulfite and pyridine.

Sythesis of **6j**.

7-Chloro-5,8-quinolinequinone [9] reacted with **1** by the similar procedure as in the condensation of **5j** with **1** giving 11-aza-5*H*-pyrido-[2,3-*a*]phenoxazin-5-one (**6k**) in the yield of 7%. Compound **6k** in acetic acid was treated with bromine at room temperature giving orange crystals which were identical with **6j**.

Compound **6k**.

This compound had ir: 1620 (C=O), cm^{-1}; uv (methanol): λ max, nm, 428, 329, 273 sh, 239.

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[10] No ^1H nmr data are available owing to the poor solubility of the compound even in a dimethyl sulfoxide-d_6 solution at 80° in an FT mode.