Synthesis of 5*H*-Pyrido[2,3-*a*]phenoxazin-5-one and 5*H*-Pyrido[3,2-*a*]phenoxazin-5-one Derivatives

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Received March 21, 1985

The 5*H*-pyrido[2,3-*a*]phenoxazin-5-one derivatives and 5*H*-pyrido[3,2-*a*]phenoxazin-5-one derivatives were prepared by the condensation of substituted 2-aminophenols with 6,7-dibromo-5,8-quinolinequinone followed by dehalogenation in the presence of sodium hydrosulfite dissolved in aqueous pyridine under a nitrogen atmosphere.

J. Heterocyclic Chem., **22**, 1483 (1985).

In view of the considerable biological and pharmaceutical activities of the iminoquinones, it is interesting to synthesize these compounds. Some phenoxazinone and phenothiazinone derivatives have been prepared as stable cyclic iminoquinones [1-5].

In this work, 5*H*-pyrido[2,3-*a*]phenoxazin-5-one derivatives **5a-c** and 5*H*-pyrido[3,2-*a*]phenoxazin-5-one derivatives **6a,b** were obtained from 4-substituted-2-aminophenols **1a-c** and 6,7-dibromo-5,8-quinolinequinone (**2**). The reaction between **1** and **2** in benzene-ethanol in the presence of anhydrous potassium acetate produces 6-bromo-10-substituted-5*H*-pyrido[2,3-*a*]phenoxazin-5-ones **3a-c** and 6-bromo-10-substituted-5*H*-pyrido[3,2-*a*]phenoxazin-5-ones **4a-c** in the ratio of about 1:1 (**3a,b:4a,b**) or 2:5 (**3c:4c**). The dehalogenation of the compounds **3** and **4** in the presence of sodium hydrosulfite dissolved in aqueous pyridine under nitrogen atmosphere gave **5a-c** and **6a,b** respectively. However **4a,b** were less dehalogenated and **4c** was entirely unchanged under the same conditions.

The structures of **5a-c** were identified by comparing their ir, uv, nmr, ms spectra and mixed melting points with authentic samples which were prepared by the reaction of **1a-c** with 7-chloro-5,8-quinolinequinone (**7**) in the presence of potassium acetate. From this identification and the spectroscopic data as well as elemental analyses, the structures of **3a-c**, **4a-c** and **6a,b** were inferred as in Scheme I.

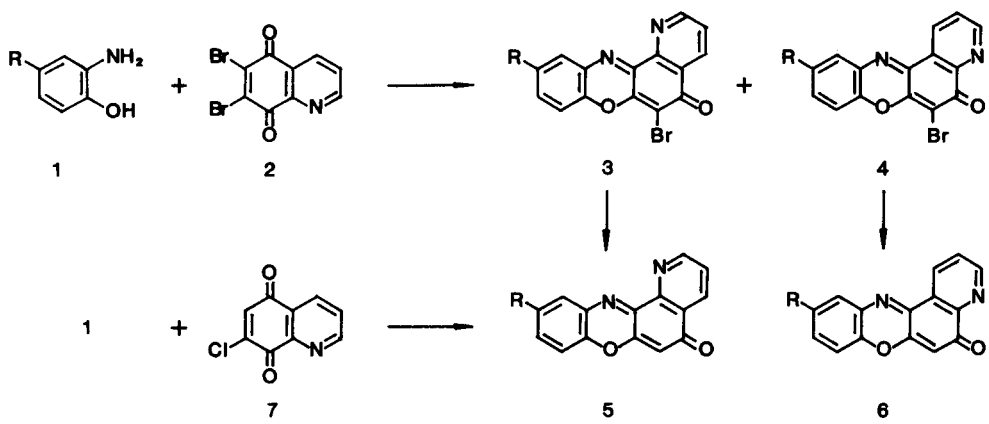
The nmr spectra of **5** and **6** exhibit a characteristic singlet at 6.5-6.7 ppm due to an olefinic proton which was substituted for the bromine atom of **3** and **4**. The signal in the lowest magnetic field is assigned to the proton on the adjacent carbon to the nitrogen in the pryidine ring of **3**, **4**, **5** and **6**.

The analytical and spectral data for the compounds obtained in these reactions are listed in Tables 1 and 2.

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 disks and the ultraviolet

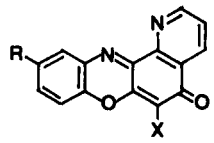
Scheme I



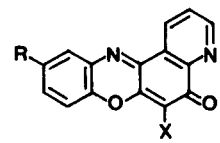
	a	b	c
R	H	CH_3	Cl

Table 1

Physical Data for Compounds **3**, **4**, **5** and **6**



3 (X=Br)
5 (X=H)



4 (X=Br)
6 (X=H)

Compound	R	Yield (%)	Mp (°C) (recrystallized)	Molecular Formula	Elemental Analyses (%) Calcd./(Found) C	H	N	Br	Cl
3a	H	14	284.4-285.6 (Chloroform)	$C_{15}H_7BrN_2O_2$ (327.1)	55.07 (55.29)	2.16 (2.04)	8.56 (8.33)	24.43 (24.67)	
4a	H	15	315.2-316.6 (Chloroform)	$C_{15}H_7BrN_2O_2$ (327.1)	55.07 (55.13)	2.16 (2.01)	8.56 (8.44)	24.43 (24.57)	
3b	CH_3	19	279.0-280.3 (Acetone)	$C_{16}H_9BrN_2O_2$ (341.2)	56.33 (56.30)	2.66 (2.53)	8.21 (8.01)		
4b	CH_3	21	278.5-279.3 (Chloroform)	$C_{16}H_9BrN_2O_2$ (341.2)	56.33 (56.51)	2.66 (2.72)	8.21 (8.12)		
3c	Cl	17	340.5-342.0 (Chloroform)	$C_{15}H_6BrClN_2O_2$ (361.6)	49.83 (50.07)	1.67 (1.58)	7.75 (7.66)	22.10 (22.36)	9.80 (9.92)
4c	Cl	44	313.5-314.5 (Chloroform)	$C_{15}H_6BrClN_2O_2$ (361.6)	49.83 (49.97)	1.67 (1.52)	7.75 (7.77)	22.10 (22.06)	9.80 (9.79)
5a	H	80	232.5-233.5 (Acetone)	$C_{15}H_8N_2O_2$ (248.2)	72.58 (72.58)	3.25 (3.21)	11.29 (11.44)		
		10 [a]							
6a	H	49 [b]	248.0-249.5 (Acetone)	$C_{15}H_8N_2O_2$ (248.2)	72.58 (72.85)	3.25 (2.98)	11.29 (11.28)		
5b	CH_3	88	249.5-250.1 (Ethyl acetate)	$C_{16}H_{10}N_2O_2$ (262.3)	73.27 (73.09)	3.84 (3.62)	10.68 (10.68)		
		7 [a]							
6b	CH_3	4 [c]	271.5-273.7 (Ethyl acetate)	$C_{16}H_{10}N_2O_2$ (262.3)			262.0743 (262.0755) [d]		
5c	Cl	87	293.3-294.5 (Chloroform-Ethyl acetate)	$C_{15}H_7ClN_2O_2$ (282.7)	63.73 (63.90)	2.50 (2.20)	9.91 (9.89)		12.54 (12.65)
		22 [a]							

[a] Obtained from **1** and **7**. [b] 45% of **4a** was recovered. [c] 40% of **4b** was recovered. [d] Exact mass spectrum was measured at Kyoto Pharmaceutical University.

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. Mass spectra were obtained with a Hitachi M-52 spectrometer. For column chromatography, alumina activated 300 (Nakarai Chemicals, Ltd.) and aluminium oxide 90 (Merck, 70-230 mesh ASTM) were used. The starting materials, *o*-aminophenol and its 4-methyl and 4-chloro derivatives **1a-c** were purchased from Nakarai Chemicals, Ltd.

General Procedure for the Preparation of 6-Bromo-10-substituted-5*H*-pyrido[2,3-*a*]phenoxazin-5-ones **3a-c** and 6-Bromo-10-substituted-5*H*-pyrido[3,2-*a*]phenoxazin-5-ones **4a-c**.

To a suspension of 6,7-dibromo-5,8-quinolinequinone (**2**) [6] (10 mmoles) and anhydrous potassium acetate (12 mmoles) in 15 ml of benzene, an alcoholic solution (30 ml) of 2-amino-4-substituted-phenol, **1a-c** (10 mmoles) was added dropwise under refluxing. After refluxing for an additional 1-3 hours with stirring, the mixture was evaporated *in vacuo*. The residue was washed with water and column chromatographed on aluminium oxide using benzene-chloroform (1:1) as the eluent. The resulting orange fraction was chromatographed on an aluminium oxide column repeatedly using benzene-chloroform (2:1-4:1) as the eluent. From the first orange-yellow fraction **3** was obtained, and then from the following orange fraction **4** was obtained.

General Procedure for the Preparation of 10-Substituted-5*H*-pyrido-[2,3-*a*]phenoxazin-5-ones **5a-c** and 10-Substituted-5*H*-pyrido[3,2-*a*]phenoxazin-5-ones **6a,b**.

A mixture of **3** or **4** (1 mmole), sodium hydrosulfite (10 mmoles), benzene (4 ml), dioxane (7 ml) and water (5 ml) was bubbled with nitrogen for 20 minutes. After reduction of the starting material, the mixture was heated to reflux. To the mixture 2.5 ml of pyridine was added and the resulting mixture was refluxed for 1-3 hours under nitrogen atmosphere. After the mixture was evaporated *in vacuo*, the residue was washed with water. Then the residue was column chromatographed on aluminium oxide using benzene-ethyl acetate (2:1) as the eluent.

Preparation of **5a-c** from **1a-c** and 7-Chloro-5,8-quinolinequinone (**7**).

An alcoholic solution of **1a-c** (1.5 mmoles) was added to a suspension of **7** [7] (1.5 mmoles) and anhydrous potassium acetate in benzene. The resulting mixture was treated as above for the preparation of **3** and **4**. Compound **5a-c** were isolated by the column chromatography on aluminium oxide using benzene-ethyl acetate (2:1-3:1) as the eluent.

Table 2

Spectroscopic Data for Compounds **3**, **4**, **5** and **6**

Compound	Mass (M^+) (relat. int. %)	IR (cm^{-1})	UV (Methanol) λ max (nm) (log ε)	^{1}H-NMR δ (ppm) [a]
3a	326/328 (100) (99)	1637 (C=O), 1618, 1579, 1548, 1287	450 (4.07), 347 (4.11), 291 (4.03), 283 (4.03), 241 (4.40)	9.21 (d, 1H, arom), 8.73 (d, 1H, arom), 8.17 (d, 1H, arom), 7.90-7.10 (m, 4H, arom)
3b	340/342 (90) (100)	1638 (C=O), 1620, 1573, 1547, 1278	464 (4.09), 349 (4.13), 294 (4.05), 245 (4.40)	9.16 (d, 1H, arom), 8.69 (d, 1H, arom), 7.91 (s, 1H, arom), 7.73 (m, 1H, arom), 7.41 (m, 2H, arom), 2.47 (s, 3H, CH_3)
3c	360/362/364 (79) (100) (24)	1640 (C=O), 1618, 1570, 1548, 1265	456 (4.05), 343 (4.13), 330 (4.14), 293 (4.12), 241 (4.41)	9.22 (d, 1H, arom), 8.75 (d, 1H, arom), 8.17 (s, 1H, arom), 7.79 (m, 1H, arom), 7.65-7.46 (m, 2H, arom)
4a	326/328 (98) (93) [b]	1640 (C=O), 1568, 1547, 1287	444 (4.15), 349 (4.15), 293 (4.08), 245 (4.51)	9.18 (bs, 1H, arom), 7.95 (d, 1H, arom), 7.58 (m, 3H, arom), 7.40-7.18 (m, 2H, arom)
4b	340/342 (100) (100)	1642 (C=O), 1568, 1550, 1280	459 (4.18), 352 (4.18), 295 (4.10), 247 (4.47)	9.13 (bs, 1H, arom), 7.73 (s, 1H, arom), 7.45 (s, 2H, arom), 7.40-7.20 (m, 2H, arom), 2.52 (s, 3H, CH_3)
4c	360/362/364 (79) (100) (30)	1647 (C=O), 1618, 1567, 1552, 1259	451 (4.14), 343 (4.20), 294 (4.18) 245 (4.52)	9.20 (bs, 1H, arom), 9.11 (bs, 1H, arom), 7.93 (s, 1H, arom), 7.82 (m, 1H, arom), 7.64-7.46 (m, 2H, arom)
5a	248 (100)	1635 (C=O), 1625, 1587, 1320	435 (4.09), 346 (4.09), 278 (4.08), 240 (4.37)	9.19 (d, 1H, arom), 8.65 (d, 1H, arom), 8.13 (d, 1H, arom), 7.74 (m, 1H, arom), 7.58 (m, 1H, arom), 7.48-7.33 (m, 2H, arom), 6.51 (s, 1H, arom)
5b	262 (100)	1635 (C=O), 1623, 1577, 1320	452 (4.18), 348 (4.19), 285 (4.17), 244 (4.46)	9.20 (bs, 1H, arom), 8.66 (d, 1H, arom), 7.93 (s, 1H, arom), 7.75 (m, 1H, arom), 7.43-7.23 (m, 2H, arom), 6.50 (s, 1H, arom), 2.47 (s, 3H, CH_3)
5c	282 (100)	1640 (C=O), 1585, 1575, 1332	442 (4.11), 339 (4.17), 329 (4.16), 284 (4.20), 244 (4.43)	(dimethyl sulfoxide-d_6), 9.14 (bs, 1H, arom), 8.53 (d, 1H, arom), 8.04 (s, 1H, arom), 7.96-7.86 (m, 1H, arom), 7.71 (m, 1H, arom), 7.57 (d, 1H, arom), 6.53 (s, 1H, arom)
6a	248 (100)	1628 (C=O), 1575, 1555, 1525, 1315	428 (4.18), 347 (4.13), 285 (4.12), 240 (4.46)	9.21 (bs, 1H, arom), 7.91 (d, 1H, arom), 7.59 (m, 2H, arom), 7.43 (m, 3H, arom), 6.73 (s, 1H, arom)
6b	262 (100)	1640 (C=O), 1578, 1558, 1320	447, 349, 289, 244	(Dimethyl sulfoxide-d_6), 9.0 (br, 2H, arom), 8.03-7.86 (m, 1H, arom), 7.73 (s, 1H, arom), 7.45 (m, 2H, arom), 6.56 (s, 1H, arom), 2.49 (s, 3H, CH_3)

[a] Deuteriochloroform was used as the solvent unless otherwise noted. s = singlet, d = doublet, m = multiplet, br = broad and bs = broad singlet.
[b] Base peak: 247 $(M-Br)^+$

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