Synthesis of Some 5H-Benzo[a]phenoxazin-5-one Derivatives

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The substituted 6-bromo and 6-chloro-5*H*-benzo[a]phenoxazin-5-ones, prepared by condensation of substituted 2-aminophenols with 2,3-dibromo or 2,3-dichloro-1,4-naphthoquinone in methanolic potassium hydroxide solution, have been dehalogenated to substituted 5*H*-benzo[a]phenoxazin-5-ones in the presence of sodium hydrosulfite dissolved in aqueous pyridine under nitrogen atmosphere.

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Although benzophenoxazones are receiving special attention, their synthetic methods described to date are considerably tedious (1-5). We previously reported that 6-alkylthio- and 6-phenylthio-5H-benzo[a]phenoxazin-5-ones were prepared by the photochemical reaction of 5H-benzo[a]phenoxazin-5-one with alkylthiols and thiophenol (6). In view of a potential interest for this class of compounds in pharmacology, we report a novel route for the synthesis of some 5H-benzo[a]phenoxazin-5-one derivatives.

In this work, 5H-benzo[a]phenoxazin-5-one and its 10-chloro and 10-methyl derivatives (4a-c) could be prepared by modified dehalogenation of their 6-bromo or 6-chloro derivatives (3a-f), which were prepared by condensation of

substituted 2-aminophenols (1a-c) with 2,3-dibromo- or 2,3-dichloro-1,4-naphthoquinone (2a,b) in methanolic potassium hydroxide solution at room temperature. It is worthy to note that, by condensation of 2-aminophenol (1a) with 2,3-dichloro-1,4-naphthoquinone (2b) in pyridine or in refluxing methanolic potassium hydroxide solution, 6-chloro-5*H*-benzo[a]phenoxazin-5-one (3d) was obtained instead of 5*H*-benzo[a]phenoxazin-5-one (4a) described by VanAllan (7). We have prepared the compound 3a by condensation of 2-aminophenol (1a) with 2,3-dichloro-1,4-naphthoquinone (2b): (a) in the presence of anhydrous potassium acetate in refluxing benzene; and (b) in methanolic potassium hydroxide solution at room temperature.

Table 1
Physical Properties of 5H-Benzo[a]phenoxazin-5-one Derivatives

Compound	X	Y	Procedure Yield, %	Mp °C	Molecular Formula	Elemental Analysis Analysis Calcd. (Found)		
No.								
						. С	Н	N
3a	Br	Н	42	196-197	$C_{16}H_8BrNO_2$	58.92	2.47	4.29
					(326.1)	(59.19)	(2.63)	(4.09)
3 b	Br	Cl	82	240-241	C ₁₆ H ₂ BrCINO ₂	53.29	1.96	3.88
					(360.6)	(53.19)	(2.03)	(3.79)
3c	Br	CH,	43	222-223	$C_{17}H_{10}BrNO_2$	60.02	2.96	4.12
		5			(340.2)	(60.20)	(2.94)	(4.19)
3d	Cl	H	A, 60	209-210	$C_{16}H_8CINO_2$	68.22	2.86	4.97
			B, 95		(281.7)	(68.17)	(2.68)	(4.95)
3e	Cl	Cl	64	251-252	$C_{16}H_7Cl_2NO_2$	60.79	2.23	4.43
					(316.1)	(60.91)	(2.16)	(4.44)
3f	Cl	CH ₃	37	240-241	$C_{17}H_{10}CINO_2$	69.05	3.41	4.74
		•			(295.7)	(68.70)	(3.53)	(4.57)
4a	Н	H	70 (a)	201-202	$C_{16}H_9NO_2$	77.72	3.67	5.67
			97 (b)		(247.3)	(77.55)	(3.54)	(5.84)
4b	Н	Cl	60 (a)	245-246	C ₁₆ H ₈ ClNO ₂	68.22	2.86	4.97
			98 (b)		(281.7)	(68.18)	(2.63)	(4.99)
4c	Н	CH ₃	86 (a)	211-212	$C_{17}H_{11}NO_2$	78.15	4.24	5.36
		· ·	98 (b)		(261.3)	(78.60)	(4.11)	(5.31)

⁽a) Compound was obtained by dehalogenation of 10-substituted 6-chloro-5H-benzo[a]phenoxazin-5-ones. (b) Compound was obtained by dehalogenation of 10-substituted 6-bromo-5H-benzo[a]phenoxazin-5-ones.

Scheme I

The dehalogenation of the compound 3 easily proceeded in the presence of sodium hydrosulfite dissolved in aqueous pyridine under nitrogen atmosphere. The reactions investigated are summarized in Scheme I. The structures of the compounds 3 and 4 were determined by elemental analysis and from spectroscopic data. In particular, the nmr spectrum (deuteriochloroform) of 4 exhibited a characteristic singlet at 6.30 ppm due to an olefinic proton, but that of 3 did not show any evidence assigned to this kind of proton. The analytical and spectral data for the derivatives obtained are listed in Tables I and II.

The present report offers a facile method for the syntheses of 5*H*-benzo[*a*]phenoxazin-5-one derivatives from readily available starting materials.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. The infrared spectra were recorded on a Jasco DS 701G spectrometer. Absorption frequencies are equated in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on a Hitachi R-20B spectrometer using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra were determined on a Hitachi M-52 spectrometer.

General Procedure for the Preparation of 6,10-Substituted 5H-Benzo-[a]phenoxazin-5-ones (3a-c,e-f).

A mixture of 2,3-dibromo- or 2,3-dichloro-1,4-naphthoquinone (2a,b) (50 mmoles), substituted 2-aminophenols (1a-c) (50 mmoles), and potassium hydroxide (2.81 g, 50 mmoles) in 150 ml of methanol was stirred for 3 hours at room temperature. The resulting precipitate was collected, washed well with water and 5% aqueous hydrochloric acid and recrystallized from benzene.

Table 2
Spectroscopic Data of 5H-Benzo[a]phenoxazin-5-one Derivatives

Compound	Mass	Infrared Spectrum	'H Nmr Spectrum (Deuteriochloroform)
No.		cm ⁻¹	ppm
3a	325 (M ⁺)	1638 (C=O); 1599; 1581; 15 1297; 1008; 765; 708	560; 7.18-7.77 (m, 6H, aromatic), 8.05-8.24 (m, 1H, aromatic), 8.38-8.59 (m, 1H, aromatic)
3b	359 (M ⁺)	1640 (C=O); 1600; 1580; 15 1270; 1010; 782; 704	563; 7.26-7.76 (m, 5H, aromatic), 8.10-8.34 (m, 1H, aromatic), 8.43-8.64 (m, 1H, aromatic)
3c	339 (M*)	1640 (C=O); 1599; 1580; 15 1286; 1008; 789; 707	564; 2.35 (s, 3H, CH ₃), 7.10-7.72 (m, 5H, aromatic), 8.08-8.30 (m, 1H, aromatic), 8.38-8.59 (m, 1H, aromatic)
3d	281 (M*)	1643 (C=O); 1605; 1594; 15 1320; 998; 768; 718	586; 7.21-7.83 (m, 6H, aromatic), 8.10-8.34 (m, 1H, aromatic), 8.46-8.70 (m, 1H, aromatic)
3 e	315 (M*)	1657 (C=O); 1597; 1583; 15 1305; 1018; 767; 704	564; 7.28-7.74 (m, 5H, aromatic), 8.07-8.38 (m, 1H, aromatic), 8.43-8.70 (m, 1H, aromatic)
3f	295 (M*)	1661 (C=O); 1616; 1601; 15 1305; 1035; 762; 702	584; 2.40 (s, 3H, CH ₃), 7.16-7.78 (m, 5H, aromatic) 8.05-8.35 (m, 1H, aromatic), 8.43-8.70 (m, 1H, aromatic)
4a	247 (M*)	1640 (C=O); 1603; 1587; 15 1314; 1000; 762; 711	568; 6.30 (s, 1H, aromatic), 7.15-7.77 (m, 3H, aromatic), 8.07-8.28 (m, 1H, aromatic), 8.48-8.67 (m, 1H, aromatic)
4b	281 (M*)	1652 (C=O); 1601; 1584; 15 1318; 1000; 794; 747; 718	572; 6.30 (s, 1H, aromatic), 7.10-7.82 (m, 6H, aromatic), 8.03-8.28 (m, 1H, aromatic), 8.45-8.71 (m, 1H, aromatic)
4c	261 (M ⁺)	1637 (C=0); 1600; 1587; 15 1319; 1000; 793; 754; 718	567; 2.40 (s, 3H, CH ₃), 6.30 (s, 1H, aromatic), 7.04-7.71 (m, 6H, aromatic), 8.04-8.29 (m, 1H, aromatic), 8.44-8.67 (m, 1H, aromatic)

The preparation of 6-chloro-5*H*-benzo[a]phenoxazin-5-one (3d).

Method A.

To a refluxing suspension of 2,3-dichloro-1,4-naphthoquinone (2b) and anhydrous potassium acetate (5.89 g, 60 mmoles) in 80 ml benzene was added dropwise with stirring an alcoholic solution of 2-aminophenol (1a) (5.45 g, 50 mmoles). After refluxing and stirring for an additional 3 hours, the mixture was cooled to room temperature. The precipitate formed was collected, washed well with water and recrystallized from benzene.

Method B.

6-Chloro-5*H*-benzo[a]phenoxazin-5-one (3d) was prepared by condensation of 1a with 2b just as was 3a.

General Procedure for the Preparation of 10-Substituted 5H-Benzo-[a]phenoxazin-5-ones (4a-c).

A suspension of 6,10-substituted 5*H*-benzo[a]phenoxazin-5-ones (3a-f) (10 mmoles), sodium hydrosdulfite (15.1 g, 100 mmoles), benzene (10 ml) and dioxane (20 ml) in 30 m,1 of water was bubbled with nitrogen for 20

minutes. After reduction of the starting materials, the suspension was then heated to reflux. At the beginning of the refluxing, 25 ml of pyridine was added to the mixture and the refluxing was continued for 3 hours under nitrogen atmosphere. After removal of the organic solvents under reduced pressure, the precipitate was collected, washed well with water and 5% aqueous acetic acid and recrystallized from benzene.

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