Synthesis of 1- and 4-Substituted-5*H*-benzo[*a*]phenoxazin-5-ones

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The 1- and 4-substituted-5*H*-benzo[*a*]phenoxazin-5-ones (substitutents: nitro, amino and acetylamino) were prepared by the condensation of *o*-aminophenol with 5-substituted-2,3-dichloro-1,4-naphthoquinones. The resulting compounds were subjected to reduction, acetylation and dehalogenation.

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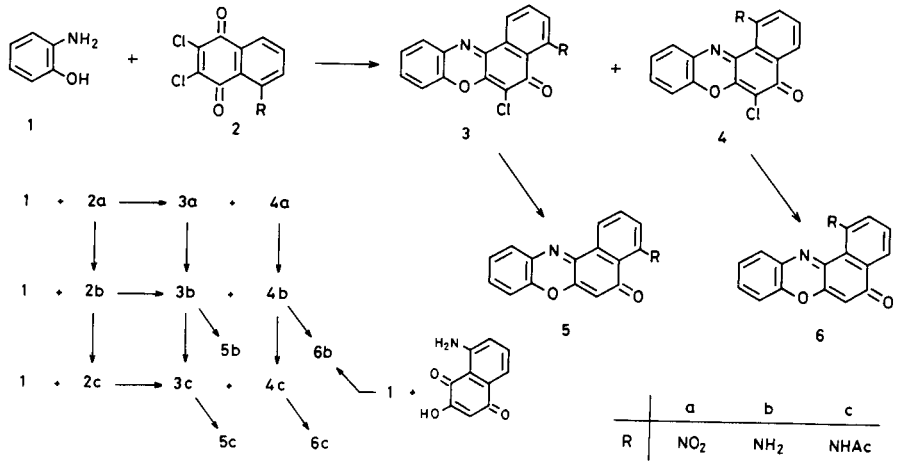
Quinone imines are useful for dyestuffs, medicines and others in the wide field of industries. Some phenoxazone and phenothiazone derivatives containing stable quinone imine systems have been synthesized to study the biological and pharmaceutical activities, *e.g.* antitumor activities, and to obtain the useful pigments [1-6].

In this work, we synthesized 4-substituted-5*H*-benzo[*a*]phenoxazin-5-ones **3a-3c** and 1-substituted-5*H*-benzo[*a*]phenoxazin-5-ones **4a-4c** (substituents: nitro group (**a**), amino group (**b**) and acetylamino group (**c**)) by the condensation of *o*-aminophenol (**1**) and 5-substituted-2,3-dichloro-1,4-naphthoquinones **2a-2c**. The conversion of the substituents of the resulting products, the reduction and the acetylation, and the dehalogenation were carried out.

The condensations between **2a-c** and **1** were carried out in dimethylformamide (DMF)/benzene or in DMF alone in the presence of anhydrous sodium acetate. The reaction of **1** and **2a** or **2c** proceeded easily at room temperature (**2a**) or 60° (**2c**), giving **3** and **4** in 88% (**2a**) or 94% (**2c**) yield, while the reaction of **2b** and **1** at 60° gave **3b** and **4b** in only 27% yield. This difference in the reactivity between **2a**, **2c** and **2b** may depend on the properties of the substituents at the 5-position. The compounds **2a** and **2c** have the electron-drawing nitro and acetylamino groups, so the electron density on the points of nucleophilic attack may be lower than that of **2b** which have the electron-donating amino group. The ratios between the products **3**:**4** were 2:1 (**a**), 1:1 (**b**) and 7:2 (**c**). They may also be attributed to the properties of the substituents. The relationships between the reactivity and the substituents are subject to the further investigation.

The reduction of the compounds **3a** and **4a** in methanol in the presence of stannous chloride and hydrochloric acid at 50° afforded **3b** and **4b** in 96% yield, respectively.

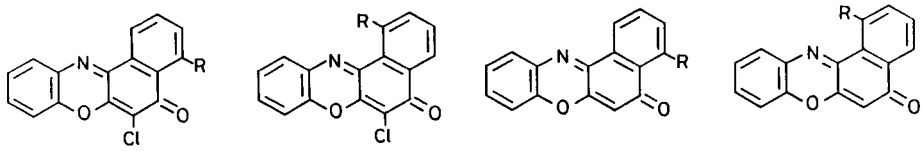
The dehalogenation of the compounds **3a-3c** and **4a-4c** were carried out in aqueous pyridine in the presence of sodium hydrosulfite under nitrogen atmosphere. Dehalogenating the compounds **3b**, **3c**, **4b** and **4c** gave **5b**, **5c**, **6b** and **6c** in 88%, 94%, 87% and 85% yield, respectively. In the case of **3a** a mixture of reduction product **3b** and reduction-dehalogenation product **5b** was obtained; the nitro group was preferentially reduced to amino group under the same condition. From **4a** a mixture of **4b** and **6b** was also obtained. The ^{1}H nmr spectra of these compounds showed singlets at 6.28, 6.44, 6.32 and 6.46 ppm characteristic to an olefinic proton at the 6-position where is substituted for the chlorine atom of **3b**, **3c**, **4b** and **4c**.



Scheme 1

Table 1

Analytical Data for **3**, **4**, **5** and **6**



3 4 5 6

Compound	R	X	Mp (°C) (recrystallized	Molecular Formula	Mass (M^+)	Elemental Analyses (%) Found/(Calcd.)		
						C	H	N
3a	NO_2	Cl	328.2-329.5 (Benzene)	$C_{16}H_7ClN_2O_4$ (326.7)	328/326	58.95 (58.82)	2.01 (2.16)	8.61 (8.57)
3b	NH_2	Cl	266.0-268.0 (Benzene)	$C_{16}H_9ClN_2O_2$ (296.7)	298/296	64.84 (64.77)	3.00 (3.06)	9.41 (9.44)
3c	NHAc	Cl	302.0-304.0 (Benzene)	$C_{18}H_{11}ClN_2O_3$ (338.7)	340/338	63.95 (63.82)	3.09 (3.27)	8.27 (8.27)
4a	NO_2	Cl	240.6-241.8 (Benzene)	$C_{16}H_7ClN_2O_4$ (326.7)	328/326	58.85 (58.82)	2.07 (2.16)	8.54 (8.57)
4b	NH_2	Cl	300.0-302.5 (Benzene)	$CC_{16}H_9ClN_2O_2$ (296.7)	298/296	64.66 (64.77)	2.98 (3.06)	9.14 (9.44)
4c	NHAc	Cl	311.3-312.5 (Benzene-Ethyl acetate)	$C_{18}H_{11}ClN_2O_3$ (338.7)	340/338	63.76 (63.82)	3.15 (3.27)	7.90 (8.27)
5b	NH_2	H	248.0-249.0 (Benzene)	$C_{16}H_{10}N_2O_2$ (262.3)	262	73.44 (73.27)	3.79 (3.84)	10.47 (10.68)
5c	NHAc	H	250.5-253.0 (Benzene)	$C_{18}H_{12}N_2O_3$ (304.3)	304	71.21 (71.05)	3.83 (3.97)	9.09 (9.21)
6b	NH_2	H	284.7-286.4 (Benzene-Acetonitrile)	$C_{16}H_{10}N_2O_2$ (262.3)	262	73.07 (73.27)	3.81 (3.84)	10.43 (10.68)
6c	NHAc	H	306.8-307.7 (Benzene-Ethyl acetate)	$C_{18}H_{12}N_2O_3$ (304.3)	304	71.48 (71.05)	3.89 (3.97)	9.22 (9.21)

For determination of the structures of **3**, **4**, **5** and **6** compound **6b** was identified with the authentic sample, 1-amino-5*H*-benzo[*a*]phenoxazin-5-one, which was prepared by the reaction of 8-amino-2-hydroxy-1,4-naphthoquinone with **1** in aqueous acetic acid by the comparison of the ir and mass spectra and the mixed melting point with those of **6b**. From this identification and the spectroscopic data as well as elemental analyses, the structures of **3**, **4**, **5** and **6** are inferred as Scheme 1.

All acetylamino compounds **3c**, **4c**, **5c** and **6c** were also obtained by the acetylation of **3b**, **4b**, **5b** and **6b**, respectively. These compounds have a broad singlet at 12.48-13.34 ppm in the lower magnetic field assigned to the N-H proton of acetylamino group.

The analytical data for the compounds obtained in these reactions are listed in Table 1.

EXPERIMENTAL

The melting points were determined on a Yanagimoto micro melting point apparatus (below 300°) and a Mitamura Riken Kogyo MEL-TEMP (above 300°). The infrared spectra were recorded on a JASCO A-102 spectrometer for potassium bromide disks. The nuclear magnetic reasonance spectra were determined on a Varian XL-200 spectrometer using tetramethylsilane as an internal reference. The mass spectra were measured on an ESCO EMD-05B spectrometer. For the column chromatography, Aluminium oxide 90 (Merck, 70-230 mesh ASTM) and Kieselgel 60 (Merck, 70-230 mesh ASTM) were used. The spectroscopic data are reported as follows: for ir spectra, wavelength (cm^{-1}), assignment; for ^1H nmr, chemical shift (δ in ppm), multiplicity (s = singlet, d = doublet, m = multiplet, br = broad), integration, assignment (this term was omitted for aromatic proton).

Condensation of 2,3-Dichloro-5-nitro-1,4-naphthoquinone (**2a**) [7] with *o*-Aminophenol (**1**).

To a stirred suspension of **1** (1.09 g, 10 mmoles) and anhydrous potassium acetate (1.64 g, 20 mmoles) in 4 ml of dimethylformamide (DMF) was added dropwise a solution of **2a** (1.36 g, 5 mmoles) in 5 ml of benzene over 20 minutes. After stirring at room temperature for additional 20 minutes, the mixture was filtered. The precipitate was washed with water, and recrystallized from benzene to give 420 mg of 6-chloro-4-nitro-5*H*-benzo[*a*]phenoxin-5-one (**3a**). The filtrate of the mixture was diluted with benzene and extracted with water to exclude DMF. The benzene layer was dried and evaporated under reduced pressure. The residue was chromatographed on an aluminium oxide column using benzene as the eluent. From the first orange fraction 960 mg of 6-chloro-1-nitro-5*H*-benzo[*a*]phenoxazin-5-one (**4a**), and from the second orange fraction 70 mg of **3a** were obtained. The total yield of the products was 88% in ratio of 2:1 (**3a**:**4a**).

Compound **3a**.

This compound had ir: cm^{-1} 1636 (C=O), 1536 and 1375 (NO_2); ^1H nmr (dimethylsulfoxide-d_6): 90° δ 8.93 (dd, 1H), 8.10 (d, 1H), 8.08 (s, 1H), 7.97 (d, 1H), 7.70-7.50 (m, 3H).

Compound **4a**.

This compound had ir: cm^{-1} 1646 (C=O), 1524 and 1360 (NO_2); ^1H

nmr (deuteriochloroform): δ 8.62 (dd, 1H), 7.91 (t, 1H), 7.82 (dd, 1H), 7.80 (dd, 1H), 7.63 (m, 1H), 7.49 (t,1H), 7.40 (t, 1H).

Condensation of 5-Amino-2,3-dichloro-1,4-naphthoquinone (**2b**) [7] and **1**.

A mixture of **2b** (121 mg, 0.5 mmole), **1** (164 mg, 1.5 mmoles) and anhydrous potassium acetate (164 mg, 2.0 mmoles) in 6 ml of DMF was stirred at 60° for 3 hours. After cooling the mixture was diluted with benzene and extracted with water to exclude DMF. After the benzene layer was evaporated under reduced pressure, the residue was chromatographed on a silica gel column using benzene-ethyl acetate (40:1) as the eluent. From the first violet fraction 22 mg of 4-amino-6-chloro-5*H*-benzo[*a*]phenoxazin-5-one (**3b**), and from the second brown fraction 18 mg of 1-amino-6-chloro-5*H*-benzo[*a*]phenoxazin-5-one (**4b**) were obtained. The total yield of the products was 27% in the ratio of about 1:1 (**3b**:**4b**).

Compound **3b**.

This compound had ir: cm^{-1} 3430 and 3320 (NH_2), 1604 (C=O); ^1H nmr (deuteriochloroform): δ 8.11 (dd, 1H), 7.80 (dd, 1H), 7.60-7.32 (m, 4H), 6.94 (dd, 1H), 6.72 (s, br, 2H, NH_2).

Compound **4b**.

This compound had ir: cm^{-1} 3400 and 3260 (NH_2), 1635 (C=O); ^1H nmr (deuteriochloroform): δ 7.83 (dd, 1H), 7.75 (dd, 1H), 7.60-7.30 (m, 4H arom and 2H, NH_2), 7.06 (dd, 1H).

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

To a stirred suspension of **3a** (327 mg, 1.0 mmole) in 50 ml of methanol was added a solution of stannous chloride (2.3 g, 10 mmoles) in 5 ml of hydrochloric acid at 50°. The suspension was stirred at 50° for additional 2 hours. After cooling the mixture was evaporated under reduced pressure. To the suspension of the residue in water was added a solution of ferric chloride (2.7 g, 10 mmoles) in 10 ml of water. After stirring for 30 minutes at room temperature, the product was filtered and washed with water. The yield of the violet precipitate was 96%. It was identified by comparison of its spectral data with **3b** prepared from **1** and **2b** as described above.

In the case of **4a**, the violet precipitate **4b** was obtained from the reaction mixture after cooling in a yield of 94%. From the filtrate an additional 6 mg (2%) of **4b** were obtained.

Condensation of 5-Acetylamino-2,3-dichloro-1,4-naphthoquinone (**2c**) [7] and **1**.

To a stirred suspension of **1** (164 mg, 1.5 mmoles) and anhydrous potassium acetate (164 mg, 2.0 mmoles) in 5 ml of DMF was added dropwise a solution of **2c** (142 mg, 0.5 mmole) in 10 ml of acetone at 50° over 1 hour. The mixture was stirred at 50° for additional 30 minutes. After cooling the mixture was filtered and washed with water, giving 91 mg of 4-acetylamino-6-chloro-5*H*-benzo[*a*]phenoxazin-5-one (**3c**). The filtrate was diluted with benzene and extracted with water to exclude DMF. The benzene layer was chromatographed on a silica gel column using benzene-ethyl acetate (40:1) as the eluent. From the first orange fraction 31 mg of **3c**, and from the second orange-yellow fraction 35 mg of 1-actylamino-6-chloro-5*H*-benzo[*a*]phenoxazin-5-one (**4c**) were obtained. The yield of products was 94% in the ratio of 7:2 (**3c**:**4c**).

Compound **3c**.

This compound had ir: cm^{-1} 3200 (NHC=O), 1687 (NHC=O), 1612 (C=O); ^1H nmr (deuteriochloroform): δ 12.48 (s, br, 1H, NHC=O), 9.12 (d, 1H), 8.55 (d, 1H), 7.89 (d, 1H), 7.76 (t, 1H), 7.63-7.37 (m, 3H), 2.30 (s, 3H, CH_3).

Compound **4c**.

This compound had ir: cm^{-1} 1690 (NHC=O), 1630 (C=O); ^1H nmr (deuteriochloroform): δ 13.29 (s, br, 1H, NHC=O), 9.18 (d, 1H), 8.16 (d, 1H), 7.72 (t, 1H), 7.69 (t, 1H), 7.60-7.36 (m, 3H), 2.39 (s, 3H, CH_3).

Acetylation of **3b** and **4b**.

The mixture of **3b** (0.5 mmole), 4 ml of acetic acid and 4 ml of acetic anhydride was stirred at 60° for 20 minutes. After cooling the mixture was filtered and washed with water giving the orange precipitate in 85% yield. It was identified by comparison of its spectral data with **3c** prepared from **2c** and **1** as discribed above. Similarly, **4b** was acetylated to **4c** with 94% yield.

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

A suspension of **3b** (0.5 mmole), sodium hydrosulfite (20 mmoles) and sodium acetate (10 mmoles) in a mixture of benzene (20 ml), dioxane (20 ml) and water (10 ml) was bubbled with nitrogen for 20 minutes. After reduction of the starting materials the suspension was heated to reflux. At the beginning of the refluxing 4 ml of pyridine was added to the mixture. After refluxing for 3.5 hours, the mixture was diluted with chloroform and extracted with water. The chloroform layer was evaporated under the reduced pressure. The residue was washed with water to afford 4-amino-5*H*-benzo[*a*]phenoxazin-5-one (**5b**) in the yield of 88%.

Compound **5b**.

This compound had ir: cm^{-1} 3460 and 3300 (NH_2), 1635 (C=O); ^1H nmr (deuteriochloroform): δ 8.10 (d, 1H), 7.78 (d, 1H), 7.52-7.25 (m, 4H), 6.94 (d, 1H), 6.68 (s, br, 2H, NH_2), 6.28 (s, 1H, olefinic).

Compounds **4b**, **3c** and **4c** were dehalogenated by the similar manner as discribed above to give 1-amino-5*H*-benzo[2,3-*a*]phenoxazin-5-one (**6b**), 4-acetylamino-5*H*-benzo[*a*]phenoxazin-5-one (**5c**) and 1-acetylamino-5*H*-benzo[*a*]phenoxazin-5-one (**6c**) in the yield of 94%, 87% and 85%, respectively.

Compound **6b**.

This compound had ir: cm^{-1} 3350 and 3250 (NH_2), 1637 (C=O); ^1H nmr (deuteriochloroform): δ 7.74 (dd, 1H), 7.53-7.33 (m, 4H arom and 2H, NH_2), 7.05 (dd, 1H), 6.44 (s, 1H, olefinic).

Compound **5c**.

This compound had ir: cm^{-1} 1698 (NHC=O), 1635 (C=O); ^1H nmr (deuteriochloroform): δ 12.63 (s, br, 1H, NHC=O), 9.06 (d, 1H), 8.48 (d, 1H), 7.82 (d, 1H), 7.72 (t, 1H), 7.52 (t, 1H), 7.42-7.28 (m, 2H), 6.32 (s, 1H, olefinic), 2.29 (s, 3H, CH_3).

Compound **6c**.

This compound had ir: cm^{-1} 1680 (NHC=O), 1635 (C=O); ^1H nmr (deuteriochloroform): δ 13.34 (s, br, 1H, NHC=O), 9.13 (d, 1H), 8.08 (d, 1H), 7.72 (t, 1H), 7.65 (d, 1H), 7.54 (t, 1H), 7.41-7.31 (m, 2H), 6.46 (s, 1H, olefinic), 2.38 (s, 3H, CH_3).

Acetylation of **5b** and **6b**.

Compounds **5b** and **6b** were treated with acetic anhydride by the similar manner of acetylation of **3b** and **4b** discribed above, giving **5c** and **6c** in the yield of 84% and 65%, respectively.

Synthesis of 1-Amino-5*H*-benzo[*a*]phenoxazin-5-one.

A mixture of 8-amino-2-hydroxy-1,4-naphthoquinone [8], **1** and 90% acetic was refluxed for 2 hours. After the mixture was concentrated under reduced pressure, the residue was chromatographed on a silica gel column using benzene-ethyl acetate (20:1-10:1) as the eluent. From the second brown fraction the red-violet precipitate was obtained in 17% yield. It was identified by comparison of its spectral data with **6b** prepared as above from **4b**.

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