Reaction of *o*-Aminophenol and *p*-Benzoquinone in Acetic Acid

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The reaction of *o*-aminophenol and *p*-benzoquinone in acetic acid yields phenoxazinones **1, 5** and **6**, phenoxazine **7**, triphenodioxazine **2**, ditriphenodioxazine **3** and the phenoxazinonyltriphenodioxazine **4**.

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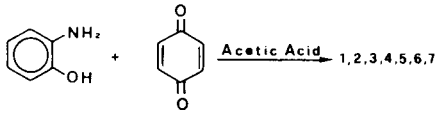
Introduction.

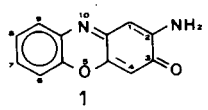
During a study on ommochrome pigments, we reported [1] that triphenodioxazine and 3*H*-phenoxazin-3-one systems are closely related. Moreover, triphenodioxazine is formed whenever *o*-aminophenol is present together with oxidizing agents [2,3]. Here we report the results of an investigation of the reaction between *o*-aminophenol and *p*-benzoquinone in acetic acid. The reaction products are characterized by elemental analysis and spectroscopic methods and a plausible mechanism for the formation of the reaction products is presented.

Results.

Treatment of an *o*-aminophenol (2 mmoles) solution in acetic acid with *p*-benzoquinone (1 mmole) at room temperature, yields after two days a complex mixture. The yellow products **1, 2, 3** and **4** were purified by chromatographic techniques and structures were established by spectral data (uv, ir, nmr, ms). Compound **1** was identified as 2-amino-3*H*-phenoxazin-3-one [2] by chromatographic and spectral comparison with an authentic sample. In addition it was converted in its acetyl derivative **1a**. While the nmr of **1** showed the C-1 proton signal at δ 6.52 ppm, it is shifted to δ 8.44 ppm in **1a** according to the strong anisotropic effect of the acetyl group. The ^{13}C spectrum and other data are communicated in the experimental section. The triphenodioxazine **2**, a yellow compound with a green fluorescence [4], is already known for about one hundred years. We prepared **2** by an unambiguous synthesis from *o*-aminophenol and 1,4-dimethoxy-*p*-benzoquinone.

Compound **3**, nearly insoluble in organic solvents, was identified to be 6,6'-ditriphenodioxazine. The mass spectrum showed the molecular ion at m/e 570 and a double charged ion at m/e 285. The ir-absorption bands at 1570 and 1468 cm^{-1} and uv absorption maxima at 506, 472 and 445 nm are characteristic for a triphenodioxazine system. The only nmr singlet at 6.40 ppm representing two protons proves the two ring systems to be linked at C-6.





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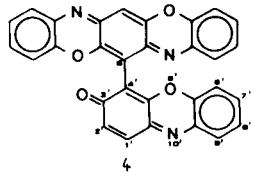

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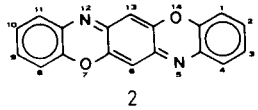

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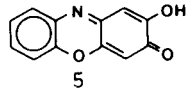

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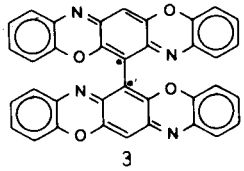

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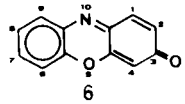

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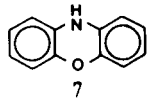

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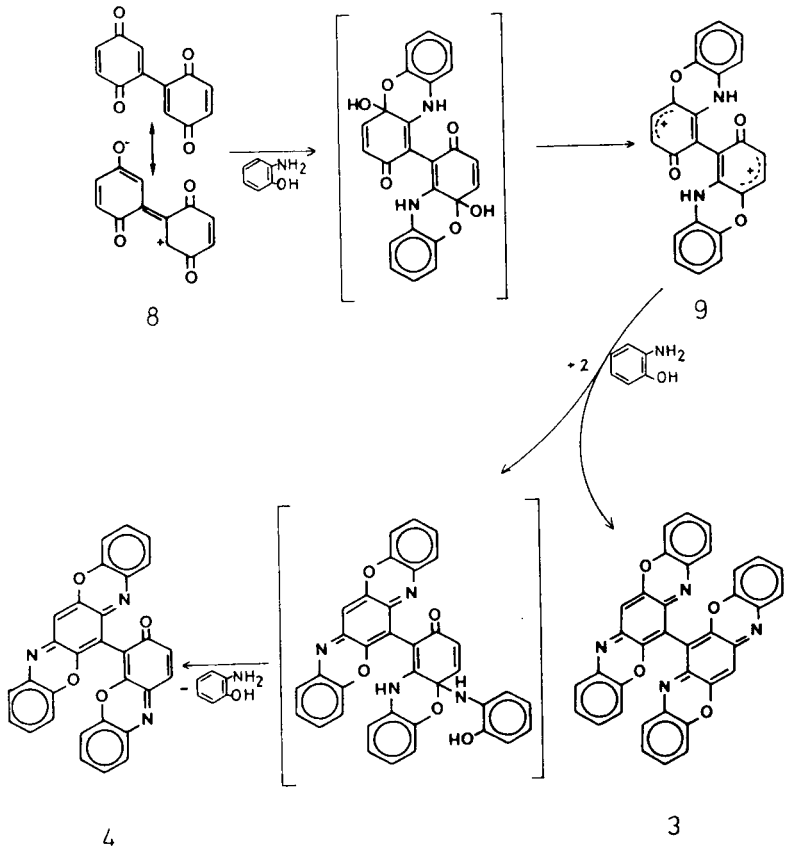
The structure of **4** was identified as 6-[4'-3*H*-phenoxazin-3-one-yl]triphenodioxazine. The ms molecular ion at m/e 481 was accompanied by an ion at m/e 483 (30% relative intensity) which must be the result of partial hydrogenation of the phenoxazinone system. The broad ir absorption at 1580 and 1465 cm^{-1} and the uv bands at 506, 472 and 440 (shoulder) nm demonstrate the presence of a triphenodioxazine ring system. This is confirmed by the nmr-spectrum which also shows two distinguishable systems of signals according to the two ring system (experimental part). The presence of the signal for *one* proton at 6.6 ppm (triphenodioxazine H-13) and the absence of a signal of H-4 of the 3*H*-phenoxazin-3-one system at 6.2 ppm, which is observed in **6**, proves the linkage of the two ring systems to be C-4/C-6.



When the reaction mixture was refluxed for 4 hours, compounds **5**, **6** and **7** were recovered in addition to **1**, **2**, **3** and **4**. 2-Hydroxy-3*H*-phenoxazin-3-one (**5**) was identified by comparison with an authentic sample [2] and in addition it was converted to the 2-methoxy derivative **5a** by use of diazomethane. In the same way the structures of 3*H*-phenoxazin-3-one (**6**) and phenoxazin (**7**) were established by comparison of spectroscopic data with those of authentic samples [5,6].

Mechanism.

Whereas the formation of **1** can be related to the oxidation of *o*-aminophenol by the present *p*-benzoquinone, the hydroxyphenoxazinone **5**, present in the refluxed mixture, is the product of hydrolysis of **1**. No trace of compound **6** could be obtained from the reaction mixture at room temperature. It seems rather to arise from the oxidation of the phenoxazine **7**, which itself is formed on heating *o*-aminophenol in a protic medium [5]. Formation of **2**, **3** and **4** are of more interest. Musso *et al.* [7] reported that triphenodioxazine is formed from hydroxy-*p*-benzoquinone and *o*-aminophenol in acidic medium and demonstrated, by labelled C and N experiments that the first step of the triphenodioxazine formation is a nucleophilic substitution of the hydroxy group of the quinone by the amino group of the aminophenol rather than a Schiff base formation. *p*-Benzoquinone does not seem to be a more suitable substrate for a Schiff base formation and *p*-benzoquinone too reacts in acetic acid according to the well established mechanisms [7] for reaction of *o*-aminophenol and hydroxybenzoquinone.

Compounds **3** and **4** do not arise from a reaction of triphenodioxazine **2**, because we found **2** to be a very stable product under the reaction conditions; we could not observe any reaction of **2** with *o*-aminophenol, *p*-benzoquinone or **1** as well as it does not yield any dimeric form. Therefore it seems reasonable that a *p*-benzoquinone dimerization reaction takes place and *o*-aminophenol subsequently reacts with the dimeric quinone. The presence of a dimeric quinone **8** in the acetic acid reaction mixture is supported by results on *p*-benzoquinone polymerization in acidic medium [8]. On the other hand a black untractable polymer and small amounts of red insoluble fractions are present in the reaction mixture. These last ones showed a typical triphenodioxazine blue color, on acid treatment [9]. When *o*-aminophenol reacts with the benzoquinone dimer **8**, an intermediate carbonium ion **9** may be formed in acidic medium. Two molecules of *o*-aminophenol react with **9** in both *para* positions of the nitrogens to give the tripheno-

dioxazine **3**. Reaction of the carbonium ion with one molecule of *o*-aminophenol followed by an aminophenol exchange reaction [10,11] with a second *o*-aminophenol yields **4**. The small amount of **4** indicates that **2** is formed from the carbonium ion faster than **4** arising from the exchange reaction.

EXPERIMENTAL

The following spectroscopic apparatus were used: Perkin-Elmer 550S spectrometer for uv , and PE-399-spectrometer for ir, Bruker 270 MHz and 500 MHz spectrometers for nmr, using tetramethylsilane as an internal reference and Varian/Finnigan CH7A and MAT-312 apparatus for ms. Melting points are uncorrected, microanalyses were performed by Divisione di Microanalisi dell'Istituto Farmacologico Italiano di Napoli. Tlc was performed on silica plates F-254, 0.25 mm with fluorescent baking (Merck).

Reaction of *o*-Aminophenol and *p*-Benzoquinone in Acetic Acid. Procedure A.

p-Benzoquinone (108 mg, 1 mmole) and 214 mg (2 mmoles) of *o*-aminophenol was added to 20 ml of glacial acetic acid. The mixture was kept at room temperature for 48 hours, neutralized with diluted sodium hydrogen carbonate, extracted with chloroform, concentrated *in vacuo*, placed on tlc plates and developed with chloroform. The chromatograms afforded four yellow products: **1** (15 mg), **2** (10 mg), **3** (33 mg) and **4** (7 mg).

Procedure B.

The reaction mixture as above was refluxed for 4 hours. Work up in the same manner yielded seven products: **1** (5 mg), **2** (10 mg), **3** (20 mg), **4** (5 mg), **5** (6 mg), **6** (2 mg) and **7** (2 mg).

2-Amino-3*H*-phenoxazin-3-one (**1**).

Following procedure A red crystals of mp 256-257° (lit [2] 256-257°) and Rf 0.5 (chloroform-methanol 97:3) were isolated; ir (chloroform): 3470-3320 cm^{-1} (NH_2), 1650 (C=O); uv (ethanol): λ max (log ε) 237 nm (4.17), 268 (3.90), 421-436 (4.10); nmr (deuteriochloroform): δ 6.44 (s, H-4, 1H), 6.52 (s, H-1, 1H), 5.16 (s, brought, exchangeable by deuterium oxide, NH_2, 2H), 7.4 (m, H-6-7-8, 3H), 7.76 (d, H-9, 1H); ms: 212 (100%, M^+), 185 (66, M-HCN).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.89; H, 3.72; N, 12.95.

2-Acetylamino-3*H*-phenoxazin-3-one (**1a**).

Fifty mg of **1** was refluxed with 5 ml of acetic anhydride and 0.3 ml of pyridine for 1 hour after the usual workup and purification on tlc-plates, 32 mg of **1a** was obtained as orange crystals mp 165° (sublimed) and Rf 0.4 (chloroform-methanol 97:3); ir (chloroform): 3360 cm^{-1}, 1690, 1600, 1560; uv (chloroform): λ max (log ε) 403 nm (4.24); proton nmr (deuteriochloroform): δ 2.13 (s, CH_3, 3H), 6.47 (s, H-4, 1H), 7.88 and 7.41 (d, H-6,9, 2H), 7.42 and 7.55 (t, H-7,8, 2H), 8.44 (s, H-1, 1H), 8.55 (s, brought, exchangeable by deuterium oxide, NH, 1H); ^{13}C-nmr: 191.598 and 169.164 (s, quinone C=O), 151.109, 147.109, 147.154, 134.096 (s, quart. C), 131.804 (d, C-1), 130.185 (d, C-8), 116.113 (d, C-7), 131.910 (d, C-5), 111.842 (s, quart. C), 104.064 (d, C-4), 24.803 (9, CH_3).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.21; H, 3.98; N, 10.98.

Triphenodioxazine (**2**).

From the reaction procedure A red crystals of mp >300° and Rf 0.7 (chloroform) were obtained; ir (potassium bromide): 1570, 1468 cm^{-1}; uv (chloroform): λ max (log ε) 443 (shoulder) nm, 471 (4.61), 505 (4.74); nmr (tetradeuterioacetic acid): δ 7.78 (d, H-4,11, 2H), 7.50 (t, H-2,9, 2H), 7.42 (t, H-3,10, 2H), 7.37 (d, H1,8, 2H), 7.01 (s, H-6, 13, 2H); ms: 286 (100%, M^+), 143 (26, M^{++}) 257 (9, M-CHO), 229 (8, M-(CHO + CO)).

Anal. Calcd. for $C_{18}H_{10}N_2O_2$: C, 75.51; H, 3.52; N, 9.79. Found: C, 75.43; H, 3.50; N, 9.82.

6,6'-Ditriphenodioxazine (**3**).

From the reaction mixture according to procedure A red crystals of mp >300° and Rf 0.7 (chloroform) were isolated; ir (potassium bromide): 1570, 1468 cm^{-1}; uv (chloroform): λ max (log ε) 455 (shoulder) nm, 472 (4.78), 506 (4.86); nmr (deuteriochloroform): δ 6.4 (s, H-13,13', 2H), 6.9 (d, H-4,8,4',8', 4H), 7.1 (m, H-2,3,9,10,2',3',9',10', 8H), 7.48 (d, H-1,11,1',11', 4H); ms: 570 (100%, M^+), 285 (14, M^{++}), 542 (16, M-CO), 271 (32, $(M-CO)^{++}$), 541 (10, M-CHO), 270.5 (8, $(M-CHO)^{++}$), 513 (8, M-(CHO + CO)).

Anal. Calcd. for $C_{36}H_{18}N_4O_4$: C, 75.80; H, 3.18; N, 9.82. Found: C, 75.78; H, 3.13; N, 9.79.

6-[4'-3*H*-Phenoxazin-3-one-yl]triphenodioxazine (**4**).

Compound **4** was obtained as yellow crystals of mp 305° and Rf 0.6 (chloroform-methanol 97:3); ir (chloroform): 1580 (broad) cm^{-1}, 1465: uv (chloroform): λ max (log ε) 440 nm (shoulder), 472 (4.25), 506 (4.32); nmr (deuteriochloroform): δ 6.60 (s, H-13, 1H), 6.88 (dd, H-1,8, 2H), 7.18 (m, H-2,3,9,10, 4H), 7.48 (d, H-4,11, 2H), 7.03 (d, J = 9 Hz, H-2', 1H), 7.19 (m, H-6',7', 2H), 7.38 (t, H-8', 1H), 7.63 (d, J = 9 Hz, H-1',or H-9', 1H), 7.87 (d, H-1' or H-9', 1H); ms: 481 (100%, M^+), 483 (30, M + 2H), 453 (18, M-CO), 452 (20, M-CHO), 424 (12, M-(CHO + CO)).

Anal. Calcd. for $C_{30}H_{15}N_3O_4$: C, 74.83; H, 3.14; N, 8.73. Found: C, 74.76; H, 3.12; N, 8.69.

2-Hydroxy-3*H*-phenoxazin-3-one (**5**).

From the compound mixture according to procedure B **5** was isolated as red crystals of mp 264-265° dec (lit [2] 264°) and Rf 0.4 (chloroform-methanol 97:3); ir (chloroform): 3500 cm^{-1}, 1670; uv (ethanol): λ max (log ε) 223 nm (4.20), 400 (4.09); nmr (deuteriochloroform): δ 6.41 (s, H-4, 1H), 6.87 (s, H-1, 1H), 7.48 (m, H-6,8, 2H), 7.61 (t, H-7, 1H), 7.98 (d, H-9, 1H); ms: (100, M^+), 185 (80, M-C=O).

Anal. Calcd. for $C_{12}H_7NO_2$: C, 67.60; H, 3.31; N, 6.57. Found: C, 67.56; H, 3.25; N, 6.42.

2-Methoxy-3*H*-phenoxazin-3-one (**5a**).

Reaction of **5** with diazomethane yielded **5a** as pale yellow crystals of mp 255° dec (lit [2] 255°) and Rf 0.7 (chloroform-carbon tetrachloride 80:20); ir (chloroform): 1750 cm^{-1}, 1610, 1570; uv (chloroform): λ max (log ε) 434 nm (shoulder), 376 (3.28); nmr (deuteriochloroform): δ 3.95 (s, CH_3, 3H), 6.40 (s, H-4, 1H), 6.63 (s, H-1, 1H), 7.78 (d, H-6, 1H), 7.49 (t, H-9, 1H), 7.38 (m, H-7,8, 2H); ms: 227 (100, M^+), 198 (75, M-CHO).

Anal. Calcd. for $C_{13}H_9NO_3$: C, 68.72; H, 3.99; N, 6.17. Found: C, 68.69; H, 3.92; N, 6.21.

3*H*-Phenoxazin-3-one (**6**).

From the reaction procedure B **6** was obtained as yellow crystals of mp 205-207° and Rf 0.7 (chloroform-methanol 87:3); ir (chloroform): 1670 cm^{-1}; uv (ethanol): λ max (log ε) 244 nm (4.1), 263 (3.8), 348 (3.9), 449 (3.95); nmr (deuteriochloroform): δ 6.2 (s, H-4, 1H), 6.87 (d, H-1, 1H), 7.35 (m, H-7,8, 2H), 7.50 (d, H-2, 1H), 7.60 (t, H-9, 1H), 7.87 (d, H-6, 1H); ms: 197 (100%, M^+), 169 (66, M-28).

Anal. Calcd. for $C_{12}H_7NO_2$: C, 73.07; H, 3.58; N, 7.10. Found: C, 72.97; H, 3.49; N, 6.88.

Phenoxazine (**7**).

From the product mixture according to procedure B **7** was isolated as colorless crystals mp 153-154° and Rf 0.6 (chloroform-carbon tetrachloride 80:20); ir (chloroform): 3320 cm^{-1}, 1450; uv (ethanol): λ max (log ε) 239 nm (4.6), 318 (3.9); nmr (deuterioacetone): δ 6.48 (d, H-4,6, 2H), 6.70 (t, H-3,7, 2H), 6.60 (d, H-2,8, 2H), 6.53 (t, H-1,9, 2H), 7.15 (s, brought, exchangeable by deuterium oxide, NH, 1H); ms: 183 (100%, M^+), 154 (63, M-29).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.75; H, 4.95; N, 7.65. Found: C, 78.69; H, 5.00; N, 7.59.

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