Synthesis of a New Diels-Alder Quinone Adduct and Its Use in Preparing Thiazolo- and Oxazoloquinolines†

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Syn (or anti) cinnamaldehydeoxime (1a, b) undergoes Diels-Alder addition to tetrabromo-p-benzoquinone (2) in dry xylene in 1 : 1 and 2 : 1 molar ratios to give the mono- and diadducts 3 and 4a, b respectively. The reaction of 3 with thioamides in ethanol gave thiazoloquinoline diones 6a-d, whereas with acid amides in ethylene glycol, it gave oxazoloquinolinodiones 12a-f.

Key Words : Cinnamaldehydeoxime, Bromanil, Monoadduct, Thiazoloquinolines, Oxazoloquinolines

Introduction

Many reports ascribe interesting biological activities to quinones and their derivatives, especially those containing fused heterocyclic rings.† Thus, among quinones, naphthoquinones have been found to possess good fungicidal‡ as well as antimalarial activities.‡ On the other hand, quinones fused to oxazole or thiazole nuclei have been endowed with good bactericidal activity.§ These interesting properties have encouraged the present studies to prepare previously unreported thiazoloquinolinodiones and oxazoloquinolinodiones, some or all of which may be associated with interesting biological properties.

Diels-Alder reaction of syn (or anti) cinnamaldehydeoxime 1a (or 1b) with bromanil (2) in a 1 : 1 molar ratio in boiling dry xylene for 30 hours afforded the monoadduct 3. The chemical structure of compound 3 is based on both elemental and spectral analyses. Its mass spectrum of electron impact did not show a molecular ion peak, but showed peaks corresponding to cinnamaldehydeoxime (1) and bromanil (2), indicating that a retro Diels-Alder reaction‡ has occurred to 3. Five peaks corresponding to the molecular ion of bromanil appeared in the mass spectrum at m/z 419.5 (0.1%), 421.5 (17.29%), 423.6 (66.72%), 425.5 (100%) and 427.6 (62%). These fit with the 5 possible ratios of isotopic 79Br and 81Br, namely 0 : 4, 1 : 3, 2 : 2, 3 : 1 and 4 : 0, respectively.

Repeating the mass spectra of the monoadduct 3 under FAB conditions showed peaks corresponding to fragment ions resulting from retro Diels-Alder reaction.‡

Repeating the reaction of the diene 1 with bromanil (2) in 2 : 1 molar ratio also preceded readily giving two products. One was dark brown and precipitated during reflux with a melting point above 360 °C; the other was light brown and was separated by concentrating the mother liquor and melts at 183 °C. The two products showed identical elemental analysis that correspond to a diadduct resulting from a (4+2) Diels-Alder addition of 2 moles of the diene to one mole of bromanil, retaining the four bromine atoms. From the theoretical point of view, the structure of the two resulting isomeric products can be represented by 4a and 4b. However, which of the two products has the higher melting point and which has the lower melting point cannot be deduced on chemical and spectral bases. Nevertheless, on the basis of observations of syn and anti isomeric compounds (e.g. syn and anti cinnamaldehydeoximes), we can unequivocally suggest that the anti-isomer (4a) is the lower-melting point compound (Scheme 2).

Similar to the monoadduct 3, the mass spectrum of the diadduct 4, did not show the molecular ion peak but showed ions corresponding to fragments resulting from retro Diels-Alder reaction, at m/z 147 (cinnamaldehydeoxime) and m/z 425.6 (bromanil). However, with the repeat of the mass

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spectra of 4 under FAB conditions, a parent ion peak at m/z 619 corresponding to the molecular ion that lost an OH group and a hydrogen bromide molecule appeared (Scheme 3).

Following our reported procedure, 10 the reaction of the monoadduct 3 with thioamides in absolute ethanol resulted in dark colored solids within 9-11 hours after the reaction commenced, with 50-75% yield. The solids were identified as dibromotetrahydroquinolino[2,3-d]thiazolediones 6a-c on basis of elemental and spectral analyses. Carrying the reaction of 3 with thioacetamide as an example for a short period (~1 hour) gave the product 5a, which could be separately transformed into 6a by refluxing in ethanol for a prolonged period (~10 hours). Therefore, 5a can be suggested to exist as an intermediate during formation of 6a (Scheme 4).

The mass spectra of compounds 6a-c were of special interest, since they fragmented in two ways. 6a (R=CH$_3$), as an example, fragmented under electron impact in two manners: in one of them it underwent retro Diels-Alder reaction as indicated by the presence of fragment ions at m/z 146.1 (1%), m/z 130.15 (28.9%), m/z 129.1 (7.7%) and m/z 103.67 (1.5%), corresponding to the cinnamaldehydeoxime that had lost a hydrogen atom, an OH group, H$_2$O molecule or H$_2$O and a cyano group, respectively, in addition to the complementary fragment ion corresponding to the dibromo-benzothiazoledione at m/z 336.23 (0.5%). In another way, 6a (R=CH$_3$) fragmented by loss of CH$_3$CN and OH groups to give three fragment ions at m/z 425.24 (100%), m/z 427.22 (64.4%) and m/z 429.23 (16.1%), containing different ratios of isotopic bromine. These successively lost HBr, Br, CO, C$_6$H$_5$ and CO to give the relatively stable fragment corresponding to pyridothiophene at m/z 132.1 (27.8%) (Scheme 5).

Dithioxamide, having two thioamido groups, also reacted
readily with the monoadduct 3 in a 1:1 molar ratio to give 7, and in a 1:2 molar ratio to give 8 (Scheme 6).

Reductive acetylation of 6a (R=CH₃), using zinc dust-acetic anhydride-fused sodium acetate mixture, gave the triacetate derivative 9, whose mass spectrum showed molecular ion peaks at m/z 614.01 (0.8%) and m/z 616.05 (4.3%), corresponding to intact molecules containing different ratios of isotopic bromine; one containing 179Br and 181Br and the other containing 281Br (Scheme 7).

Another indication of the occurrence of a retro Diels-Alder reaction of the triacetate under electron impact was obtained by observing the fragment ions at m/z 427.1 (1.9%) and m/z 189.66 (19.3%), which correspond to structures 10 and 11, respectively (Scheme 8).

The appearance of the molecular ion peak of 9 is an indication of the relative stability of the triacetate derivative as compared with the parent compound 6a, which is possibly due to the partial aromatization of the quinonoid ring.

Oxazoloquinolinediones 12a-e were prepared by interaction of 3 with acid amides in boiling ethylene glycol in the presence of bicarbonate. Following this established method of ours,¹¹ dark brown crystalline products 12a-e resulted in good yields after 8-10 hours reflux.

The structure of compounds 12a-e was determined by elemental and spectral analyses. Elemental analysis showed the absence of halogen, the IR spectra showed bands at 1650 cm⁻¹, 1600 cm⁻¹ and 1550 cm⁻¹ characteristic of an oxazole system, in addition to bands at 1670 cm⁻¹, 1100 cm⁻¹ and 755-765 cm⁻¹ characteristic of νC=O conjugated with C=C, νN-O in aromatic ring and νsadj Ar-H, respectively. Also, the mass spectrum of compound 12d (R=CH₂Ph), as an example, showed a peak at m/z 385 corresponding to M+2.

The mechanism of formation of compounds 12a-c is suggested to proceed according to Scheme 9 in which the amide undergoes a nucleophilic attack at position 2 of the adduct 3 to give an intermediate 11a-e, which undergoes dehydrobromination most likely under the influence of the basic effect of the bicarbonate and the high energy of the reaction medium to give a final mesoionic product 12a-e (Scheme 9).

An experimental proof to the involvement of 11a-e as intermediate during formation of the oxazoloquinolinedione 12a-e was approached from the separation of 11d as a minor product on dilution (with water) of the mother liquor of the reaction, together with its formation in quantitative yield on repeating the reaction between phenylacetamide and the adduct 3 for 30 minutes only, in the absence of bicarbonate. Moreover, heating 11d in ethylene glycol for ~7 hours in the presence of HCO₃⁻ transformed it into the oxazoloquinolinedione 12d in good yield. The structure of the intermediate 11d, R=CH₂Ph is based on elemental, IR and mass spectral analyses. The latter did not show a molecular ion peak at m/z 624.7 but showed a peak corresponding to M-CO at m/z 596.7 (14.0%). The mass spectrum revealed also that the compound undergoes retro Diels-Alder reaction

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**Scheme 7**

**Scheme 8**

**Scheme 9**

**Scheme 10**
under electron impact as indicated by the appearance of the two complementary fragments at m/z 147.1 (8.7%) and m/z 477.2 (13.7%), corresponding to the cinnamaldehydeoxime and 2-benzylamino-3,5,6-tribromo-p-benzoquinone (Scheme 10).

The reaction of succinamide, with the monoadduct 3 could be made to give the products 13 and 14, depending on the molar ratios of the reactants used (Scheme 11).

Antimicrobial Screening. Some of the prepared compounds possessing fair solubility in ethylene glycol were selected, and their in vitro antimicrobial activities against four strains of bacteria were determined using the filter paper disc method.\(^{(12,13)}\) These strains included Staphylococcus aureus and Staphylococcus albus as gram-positive bacteria and Salmonella and Klebsiella as gram-negative. The results obtained are included in Table 1.

These data show that with exception of Staphylococcus albus, which was lightly resistant to the majority of tested compounds, all other bacteria strains were sensitive. The sensitivity however, varied with change of both type of nucleus or substituent.

From the limited data of biological screening that we obtained, working out a correlation between structure and activity is rather difficult. However, we have concluded that the results obtained are satisfactory and encourage further synthetic studies in this field.

Experimental Section

All melting points are uncorrected and determined on a Gallenkamp apparatus with a digital thermometer type MFB-595-010M. The IR spectra were measured on an IR-470 Spectrophotometer [SHIMADZU], using the KBr Wafer technique. The mass spectra were run on a JEOLJMS600 apparatus at Assiut University. Preparation of bromanil 2 (m.p. 298-300 °C), \( \text{syn} \) cinnamaldehydeoxime (m.p. 138 °C) and \( \text{anti} \) cinnamaldehydeoxime (m.p. 64 °C) was carried out by known procedure.

Preparation of Diels-Alder monoadduct 3. Bromanil 2 (4.24 g, 0.01 mol) was dissolved in dry \( p \)-xylene (20 mL) and the solution treated with 1.47 g (0.01 mol) of the high-melting point cinnamaldehydeoxime dissolved also in dry \( p \)-xylene (20 mL). The reaction mixture was refluxed on a sand bath (at 130-145 °C) for about 20 hours, until the color of the reaction mixture changed from reddish orange to dark reddish brown, then it was cooled and filtered from any tetrabromohydroquinone formed. Concentration of the filtrate followed by cooling and the addition of few mls of petroleum ether (40-60 °C) precipitated a dark brown crystalline product that was collected and recrystallized from EtOH as deep brown fine crystals of 5\( \alpha \),6,7,8\( \alpha \)-tetrabromo-1,4,5\( \alpha \),8\( \alpha \)-tetrahydro-1-hydroxy-4-phenyl-5,8-quinoline-dione (3), m.p. 217 °C (yield 40%). Anal. Calc. for C\( _{15} \)H\( _8 \)Br\( _4 \)NO\( _3 \): C, 31.56; H, 1.58; N, 2.45; Br, 55.9. Found. C, 31.4; H, 1.34; N, 2.41; Br, 55.67.

The previous reaction was repeated under the same conditions, using low melting-point cinnamaldehydeoxime instead of the high-melting one. The product obtained was identical in all respects with that obtained from high melting-point cinnamaldehydeoxime, m.p. and mixed m.p. 247 °C.

Acetylation of the monoadduct 3, using acetic anhydride fused sodium acetate, gave a yellow-brown acetate crystalized from ethanol, m.p. 134 °C. Anal. Calc. for C\( _{17} \)H\( _{11} \)Br\( _4 \)NO\( _3 \): C, 31.56; H, 1.58; N, 2.45; Br, 55.9. Found. C, 31.4; H, 1.34; N, 2.41; Br, 55.67.

Preparation of diadducts 4a, b.

Reaction of bromanil (2) with the high melting-point cinnamaldehydeoxime (1a) in \( 2 : 1 \) molar ratios: A mixture of bromanil 2 (4.24 g, 0.01 mol) and high melting-point cinnamaldehydeoxime 1a (2.24 g, 0.02 mol) in dry \( p \)-xylene (50 mL) was refluxed on a sand bath (at 120-140 °C) for about 30 hours, with the color of the reaction mixture changing from red to dark reddish brown and a dark crystalline product separated out, which was collected by
Table 2. Reaction products from monoadduct 3 and thioamides

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Thioamide or amide used</th>
<th>Colour (time, h)</th>
<th>Solvent</th>
<th>m.p. °C (% yield)</th>
<th>Formula</th>
<th>Calculated / Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Thioacetamide</td>
<td>reddish-brown</td>
<td>ethanol</td>
<td>191 (78)</td>
<td>C$<em>{17}$H$</em>{16}$Br$_2$N$_2$O$_3$S</td>
<td>42.21 2.49 5.78 33.0 6.6</td>
</tr>
<tr>
<td>3b</td>
<td>Thiourea</td>
<td>dusty-brown</td>
<td>acetone</td>
<td>202 (63)</td>
<td>C$<em>{16}$H$</em>{16}$Br$_2$N$_2$O$_3$S</td>
<td>39.61 2.28 8.66 32.94 6.59</td>
</tr>
<tr>
<td>3c</td>
<td>Phenyli thiourea</td>
<td>light-brown</td>
<td>methanol</td>
<td>226 (35)</td>
<td>C$<em>{22}$H$</em>{18}$Br$_2$N$_2$O$_3$S</td>
<td>47.08 2.69 7.48 28.47 5.71</td>
</tr>
<tr>
<td>7</td>
<td>Dithioxamide</td>
<td>brownish-red</td>
<td>ethanolbenzene</td>
<td>169 (58)</td>
<td>C$<em>{17}$H$</em>{17}$Br$_2$N$_2$O$_3$S$_2$</td>
<td>38.58 2.09 7.94 30.20</td>
</tr>
<tr>
<td>8</td>
<td>Dithioxide</td>
<td>dark-brown</td>
<td>ethanolbenzene</td>
<td>290 (50)</td>
<td>C$<em>{32}$H$</em>{18}$Br$_4$N$_2$O$_4$S$_2$</td>
<td>40.97 1.93 5.97 34.06 6.82</td>
</tr>
</tbody>
</table>

* Ratio of monoadduct to acid amide.

filtration. The product was insoluble in all available organic solvents (benzene, ethanol, chloroform and acetic acid) and was only partially soluble in dimethyl sulphoxide. This product was purified by exhaustive boiling with benzene leaving a residual dark brown solid, which was dried and analyzed as 4a, m.p. >360 °C. Anal. Calc. for C$_{24}$H$_{18}$Br$_4$N$_2$O$_4$: C, 40.09; H, 2.57; N, 3.98; Br, 44.51. Found: C, 40.1; H, 2.7; N, 4.07; Br, 44.88.

The dark colored mother liquor of the reaction was concentrated and cooled; a light brown product precipitated, which was collected and recrystallized from benzene - petroleum ether (40-60 °C) as reddish brown micro crystals (0.57 g, 0.001 mol) was dissolved in (30 mL) of absolute EtOH and treated with 2-3 g of fused sodium acetate and ~3 mL of glacial acetic acid. The mixture was refluxed for ~2 hours. Its color gradually faded gradually to pale yellow. The reaction mixture was then treated with 2-3 g of zinc dust (or granules), 3 g of fused sodium acetate and ~3 mL of glacial acetic acid. The mixture was refluxed for about 2 hours. Its color faded gradually to pale yellow. The reaction mixture was then filtered while hot. The filtrate was cooled and diluted with ice cold water and stirred. A yellow to light brown solid separated out, which was filtered, washed with excess water, air dried and recrystallized from EtOH to give 5a, m.p. 208 °C (yield 78%). Anal. Calc. for C$_{17}$H$_{17}$Br$_2$N$_2$O$_3$S: C, 36.13; H, 2.31; N, 4.95; Br, 42.42. Found: C, 36.2; H, 2.4; N, 4.99; Br, 42.7; S, 5.8.

Transformation of N-(3,4,8α-tribromo-5-hydroxy-4α,5,8,8α-tetrahydro-1,4-dioxo-8-phenyl-2-quinolinylthioacetamide (5a) into the cyclized form (6a), Compound 5a (0.5 g) in absolute ethanol (30 mL) was refluxed for about 10 hours, and the color changed from light brown to dark reddish brown. Concentration and cooling of the reaction mixture precipitated a deep brown crystalline product that was collected and recrystallized from ethanol as a yellowish brown micro crystals of 6a, m.p. 103 °C (yield 75%). Anal. Calc. for C$_{32}$H$_{18}$Br$_4$N$_2$O$_4$: C, 42.21; H, 2.49; N, 5.78; Br, 33.0; S, 6.6. Found: C, 42.17; H, 2.56; N, 5.83; Br, 33.2; S, 6.52.

Reductive acetylation of 4α,8α-dibromo-8-hydroxy-4α,5,8,8α-tetrahydro-2-methyl-5-phenylquinolinolino[2,3-d]-thiazole-4,9-dione (9), Compound 6a (0.5 g) was dissolved in ethyl alcohol (15 mL), giving a deep brownish red solution. To this solution was added 2-3 g of zinc dust (or granules), 3 g of fused sodium acetate and ~3 mL of glacial acetic acid. The mixture was refluxed for about 2 hours. Its color faded gradually to pale yellow. The reaction mixture was then filtered while hot. The filtrate was cooled and diluted with ice cold water and stirred. A yellow to light brown solid separated out, which was filtered, washed with excess water, air dried and recrystallized from EtOH to give 9, m.p. 103 °C. Anal. Calc. for C$_{32}$H$_{26}$Br$_2$N$_2$O$_3$: C, 45.12; H, 3.29; N, 4.57. Found: C, 45.62; H, 3.47; N, 4.2.

Reaction of the monoadduct 3 with acid amides.

Description of general procedure: A mixture of the monoadduct 3 (0.57 g, 0.001 mol) and the appropriate acid amide (0.001 mol) was dissolved in (30 mL) ethylene glycol, and the solution was refluxed gently for about 2 hours. The dark colored solution was then treated with 2-3
A mixture of 11b (0.5 g) dissolved in 30 mL of ethylene glycol and the solution treated with 3 mL of 10% aqueous sodium bicarbonate. The reaction mixture was refluxed for about 8 hours, and a dark brown solid precipitated completely. The product was collected and washed with water then with hot ethanol and air dried. The compound was identified as 2-methyl-8-oxy-5-phenylquinolinolino[2,3-d]oxazole-4,9-dione, m.p. >360 °C (yield 64%).

**Antimicrobial Screening.** Bacterial species were firstly grown for 24 hours on nutrient broth of the following composition: peptone (10 g), beef extract (3 g), NaCl (5 g), and 1 liter distilled water. Then 1 mL of the broth culture was placed in a sterile plate; next, 10 mL of nutrient agar composition: peptone (10 g), beef extract (3 g), NaCl (5 g) and 1 liter distilled water. Then 1 mL of the broth culture was poured just before solidification and mixed thoroughly with bacterial inoculum. After solidification of the media in plates, filter paper discs (Whatman No. 3) of 5 mm diameter, which were previously immersed in a solution of the tested chemical compounds, were placed on the surface of the agar medium. Plates were incubated at 37 °C for 24 hours and the clear zones around the discs were measured.

**Sensitivity Test**

T able 3. Reaction products from monoadduct 3 and amides

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Thioamide or amide used</th>
<th>Colour (time, h)</th>
<th>Solvent</th>
<th>m.p. °C (% yield)</th>
<th>Formula</th>
<th>Calculated / Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>Formamide</td>
<td>dark-brown</td>
<td>insoluble</td>
<td>&gt; 360 (80)</td>
<td>C₇H₈N₂O₄</td>
<td>65.75 2.75 9.58 0.00</td>
</tr>
<tr>
<td>R=H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12b</td>
<td>Acetamide</td>
<td>dark-brown</td>
<td>insoluble</td>
<td>&gt; 360 (51)</td>
<td>C₇H₆O₄N₂</td>
<td>66.66 3.29 9.14 0.00</td>
</tr>
<tr>
<td>R=CH₃</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12c</td>
<td>Benzamide</td>
<td>light-brown</td>
<td>insoluble</td>
<td>&gt; 360 (55)</td>
<td>C₇H₆O₄N₂</td>
<td>71.63 3.28 7.60 0.00</td>
</tr>
<tr>
<td>R=Ph</td>
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<td></td>
</tr>
<tr>
<td>12d</td>
<td>Phenylacetamide</td>
<td>brown</td>
<td>insoluble</td>
<td>&gt; 360 (53)</td>
<td>C₇H₆O₄N₂</td>
<td>72.24 3.69 7.32 0.00</td>
</tr>
<tr>
<td>R=CH₃Ph</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12e</td>
<td>Urea</td>
<td>yellowish brown</td>
<td>insoluble</td>
<td>&gt; 360 (40)</td>
<td>C₇H₅N₂O₄</td>
<td>62.54 5.95 13.67 0.00</td>
</tr>
<tr>
<td>R=NH₃</td>
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<tr>
<td>13</td>
<td>Succinamide (1:1)</td>
<td>yellowish brown</td>
<td>insoluble</td>
<td>&gt; 360 (51)</td>
<td>C₇H₅N₂O₃</td>
<td>62.81 3.60 11.56 0.00</td>
</tr>
<tr>
<td>14</td>
<td>Succinamide (2:1)</td>
<td>brownish violet</td>
<td>insoluble</td>
<td>&gt; 360 (52)</td>
<td>C₇H₅N₂O₃</td>
<td>66.80 2.97 9.17 0.00</td>
</tr>
</tbody>
</table>

*Ratio of monoadduct to acid amide.

mL of 10% aqueous solution of sodium bicarbonate and reflux continued for a further 6-8 hours during which dark fine crystalline solids of the corresponding oxazoquinolinedione precipitated. These were filtered from the hot reaction mixture, washed with water and finally with ethanol (yield 40-80%). All compounds prepared were characterized by sparing solubility in most organic solvents, hence they were purified by exhaustive extraction of the impurities with suitable organic solvents, leaving analytically pure crystalline solids. Dilution of the mother liquor of the original reaction precipitated light colored products that were filtered off, recrystallized from the appropriate solvent, and identified as precipitated light colored products that were filtered off, recrystallized from the hot reaction mixture, washed with water then with ethanol and air dried. The compound was identified as 2-methyl-8-oxy-5-phenylquinolinolino[2,3-d]oxazole-4,9-dione, m.p. >360 °C (yield 64%).

**Transformation of 11b into 12b.** Compound 11b (0.5 g) was dissolved in about 30 mL of ethylene glycol and the solution treated with 3 mL of 10% aqueous sodium bicarbonate. The reaction mixture was refluxed for about 8 hours, and a dark brown solid precipitated completely. The product was collected and washed with water then with hot ethanol and air dried. The compound was identified as 2-methyl-8-oxy-5-phenylquinolinolino[2,3-d]oxazole-4,9-dione, m.p. >360 °C (yield 64%).
New Thiazolo- and Oxazoloquinolines from a Quinone Adduct

References


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