# INVESTIGATION OF HETEROCYCLIC QUINONES

## XI.\* 2-QUINOLONOQUINONES

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A general method for the synthesis of substituted 8-amino-2-quinolono-5,6-quinones by oxidation with simultaneous amination of 6-hydroxy-2-quinolones is described. The stepwise course of the process and several properties of the compounds obtained are studied.

2-Quinolonoquinones are attracting attention in connection with the search for antimalarials [1,2] and anticancer preparations [3]. The synthesis of several 2-quinolono-5,6-quinones by oxidation of 6hydroxy-2-quinolones with chromic anhydride is described in [2]. The method is not applicable to 6hydroxy-2-quinolones with labile substituents because of the severe oxidation conditions. An original synthesis of 6-hydroxy-2-quinolono-5,6-quinone was recently accomplished [3], but only quinones which are unsubstituted in the 3 and 4 positions can be obtained via the proposed scheme.

In this communication we describe the synthesis of a number of substituted 2-quinolono-5,6- and -5,8-quinones using oxidative amination of 6-hydroxy-2-quinolones with oxygen in the presence of a Cu<sup>2+</sup>- secondary amine complex [4, 5]. The use of this method has made it possible to work out a simple and universal method for the synthesis of substituted 2-quinolonoquinones. The starting substances were 6-hydroxy-2-quinolones with various substituents in the 3 and 4 positions (Ia-c). We have shown that the reaction does not proceed in the presence of catalytic amounts of cupric ions; this is apparently explained by competitive combining of the Cu<sup>2+</sup> ion with the starting compounds since the capacity of 2-quinolones to give complexes with the salts of heavy metals is well known [6]. It was found that the optimum amount of cupric acetate for the oxidation of Ia and Ib is 0.25 g-eq per mole of starting compound. The reaction proceeds very vigorously with 1 g-eq per mole, but the yield drops due to resin formation. The best yield in the oxidation of Ic in the presence of piperidine is obtained with 0.5 g-eq of cupric acetate per mole of compound, but 1 g-eq of copper salt per mole of Ic must be used for the oxidation in the presence of morpholine.

Hydroxyquinolones Ia-c are oxidized in the presence of both piperidine and morpholine. The rate and completeness of the reaction depend on the ratio of the 6-hydroxyquinolone to the secondary amine; this should be no less than 1:6-1:8 for the preparation of quinones Va, e, g, and h. The reaction rate for the oxidation of Ia and b in the presence of morpholine is extremely low. In contrast to 4-chloro-6-hydroxy-quinolines [7], the chlorine is not replaced by the secondary amine residue during oxidation of Ib. This is in good agreement with the well-known inertness of chlorine in 4-chloro-2-quinolones.

Compound I is converted into V via a series of steps [4]. In order to elucidate the role played by copper ions and amine, we obtained all the assumed intermediates (II-IV) and examined their behavior under the reaction conditions. 5,6-Dihydroxy-4-methyl-2-quinolone (IIa) was obtained by reduction of IIIa with hydrazine hydrate; this is considerably simpler than catalytic hydrogenation [2]. Secondary amines added spontaneously to quinones III; with morpholine the slightly soluble compounds IVa and IVb formed and precipitated, while the more soluble piperidine adducts are oxidized by air oxygen to the corresponding quinones. The experimental results on the oxidation of 6-hydroxy-2-quinolones and a number of intermediate

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<sup>\*</sup> For Communication X, see [10].

		Yield, %	8888	88 67 69 87 69 87 69	72	71	62 86	806 90	20	63
	Calc., %	z	10,0	10,2	11,7	12,8	8,0	10,1	8,5	8,4
		н	6,1	5,2	5,7	1	I		6,7	6,1
		U	64,0	61,3	57,6	1	1		65,4	61,7
	Found, 7/0	Z	10,1	10,4	11,4	12,9	7,9	10,3	1'8	8,2
		H	6,4	5,2	5,7	1	1		6,7	6,1
		υ	63,8	61,5	58,0	1	1 ·	1	65,2	61,8
		Empirical formula	$C_{15}H_{16}N_2O_3\cdot 1/2\ H_2O$	C14H14N2O4	G12H12N2O3 · H2O	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub>	C18H21CIN2O3 7	C17H19CIN204 ‡	C <sub>18</sub> H <sub>22</sub> N <sub>2</sub> O4	C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub>
	Spectra	λ <sub>max</sub> , (lg ε)	(4,22) (4,27) (4,14)	(4,21) (4,26) (4,16)	(4,31) (4,21) (4,05)	(4,12) (4,22) (4,22)	(4,09) (4,28) (4,20)	(4,09) (4,33) (4,18)	(4,02) (4,30) (4,05)	(4,21) (4,38) (4,08)
			240 285 370	240 284 374	242 345 345	235 280 353	244 285 380	243 295 377	$\begin{array}{c} 224 \\ 288 \\ 370 \end{array}$	222 288 373
		]R 1600–1700 cm <sup>-1</sup>	1688 s 1610 sh	1695 s 1635 s	1650 w	1680 s 1660 sh	1690 sh 1663 s 1615 s	1684 <b>s</b>	1665 sh 1645 s 1647 s	1650 m 1615 s
	mp (solvent)•		164165 (alcohol)	172-173 (alcohol)	174—175 (acetone - water)	189—190 (water)	206-207 (benzene)	163-165 (alcohol)	143144 (ethyl ace- tate_petrole- um ether)	225-227 (acetone - water)
(V)	Reaction time, min		300 15 10	20 <sup>2</sup>	15	15	240 30	30	210	180
nones	Amine, mole start.comp., ofom		8044	タター	4	4	<b>%</b> 4	41	αō.	∞
Qui	Cu(OAc)2, g-eq start.comp., nole		0,25 0,01	0,01	0,01	0,01	0,25 0,01	0,01	0,5	1,0
LE 1.	Starting compound		Ia IIa IIIa	IIa IIIa IVa	IIIa	IIIa	d III d III	d III d VI	Ic	C
TAB.	product Reaction		Va	ЧЪ	Vc	νd	Ve	Vf	V g	٨'n

\*All compounds melt with decomposition.  $\ddagger$  Found %: Cl 10.4. Calculated %: Cl 10.2.  $\ddagger$  Found %: Cl 8.0. Calculated %: Cl 8.0. compounds (Table 1) indicated that: 1) the first step – ortho hydroxylation – is rate limiting; 2) conversion of intermediates II and III to the corresponding quinones proceeds with the catalytic amount of cupric acetate, while IV is converted even in the absence of copper salt; 3) intermediates II-IV are converted to quinones V with a smaller excess of secondary amine as well as in the presence of primary amines (methylamine).



A product whose structure was not established is formed along with quinone Vd when IIIa is oxidized in the presence of methylamine. We have shown that aniline does not add to quinones III under the reaction conditions, while benzaldehyde formation and resin formation are observed in the presence of benzylamine. In this connection, it is interesting to note that the attempts of Holmes et al. [2] to isolate a product from the reaction of quinone IIIa with ammonia were unsuccessful.

Quinones V are readily soluble in weak aqueous solutions of bicarbonates and amines and are precipitated on acidification. While the acidic properties of Vg and Vh are due to the presence of a hydroxyl group at the  $C_4$  atom [8], the acidic properties of Va-Vf are due to the ease of formation of a resonancestabilized anion:



The morpholine salt of quinone Vb was isolated in the solid state. Since quinones Va-f are stronger acids than carbonic acid ( $pK_a$  6.4), their acid ionization constants are at least four orders of magnitude larger than that of 2-quinolone ( $pK_a > 11$ ) [9]. Quinones V are readily saponified to 6-hydroxy-2-quinolono-5,8-quinones (VI) by dilute alkali. The two-step process for conversion of 6-hydroxy-2-quinolones to 6-hydroxy-2-quinolono-5,8-quinones is a convenient method for obtaining these compounds.

All of the quinones described in this paper exhibit characteristic bands in the carbonyl absorption region of their IR spectra and were characterized in the form of stable phenazines (Table 2).

#### EXPERIMENTAL

4-Methyl-6-hydroxy-2-quinolone (Ia) and 3-n-Butyl-4-chloro-6-hydroxy-2-quinolone (Ib). These compounds were obtained by demethylation of the corresponding 6-methoxy-2-quinolones with sulfuric acid via the method in [8]. Compound Ia was obtained in 78% yield and had mp 314-316°, while Ib was obtained in 98% yield and had mp 214-216° [2].

<u>3-n-Butyl-4,6-dihydroxy-2-quinolone (Ic).</u> A solution of 20 g (75 mmole) of 3-n-butyl-4-hydroxy-6methoxy-2-quinolone [2] in a mixture of 150 ml of 48% HBr and 50 ml of glacial acetic acid was refluxed for 6 h. Water (300 ml) was then added with cooling and the mixture was neutralized with 40% sodium hydroxide. The resulting precipitate was separated, washed with water, and recrystallized from 230 ml of 30% alcohol to give 16.7 g (88.5%) of a crystalline, colorless substance that was soluble in alcohol, methanol, and dioxane, and insoluble in benzene, petroleum ether, and water, and had mp 234-236°. Found %: C 66.7; H 6.5; N 5.9.  $C_{13}H_{15}NO_3$ . Calculated %: C 66.9; H 6.5; N 6.0.

Comp.	R'	R″	R	Reaction medium	mp (solvent)	Empirical formula
VIIa	Н	CH₃	N (CH <sub>2</sub> ) 5	Acetic acid	267—268 (alcohol)	C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O
AIIp	н	CH₃	$N(CH_2CH_2)_2O$	Alcoho1	295—296 (alcohol)	$C_{20}H_{18}N_4O_2$
VIIc	н	CH3	N (CH <sub>3</sub> ) 2	Acetic acid	236—237 (acetone)	$C_{18}H_{16}N_4O$
VIId	Н	CH <sub>3</sub>	NHCH3	Acetic acid	300, деф. (alcohol)	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O
VIIe	n-C₄H9	Cl	N (CH <sub>2</sub> ) 5	Acetic acid	202-203	C <sub>24</sub> H <sub>25</sub> ClN <sub>4</sub> O
VII g	n-C₄H9	он	N (CH <sub>2</sub> ) 5	Acetic acid – alcohol (2:1)	(acetone)	$C_{24}H_{26}N_4O_2$
VIħ	n-C₄H9	ОН	N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	Alcohol	265-267 (benzene)	$C_{23}H_{24}N_4O_3$
VIIi	н	CH₃	ОН	Acetic acid - water	>340	$C_{16}H_{11}N_3O_2\cdot H_2O$
VIIj	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	Cl	ОН	Acetic acid	(acetic acid)	$C_{19}H_{16}CIN_3O_2$

TABLE 2. Phenazines (VII)

<u>4-Methyl-5,6-dihydroxy-2-quinolone (IIa)</u>. A suspension of 1.0 g (5.7 mmole) of IIIa [1] in 40 ml of 2% aqueous hydrazine hydrate was heated on a water bath, during which the quinone dissolved and a light-yellow precipitate formed. After 10 min the reaction mass was cooled, and the resulting precipitate was filtered and washed with water, alcohol, and ether to give 0.8 g (80%) of light-yellow crystals that were moderately soluble in methanol, alcohol, and water, slightly soluble in acetone and acetic acid, and insoluble in chloroform and ether. The substance was oxidized in air and decomposed at about 280° (crystals obtained from water in the presence of sodium hydrosulfite). Found %: C 60.5; H 5.8; N 7.2%.  $C_{10}H_9NO_3$  ·  $H_2O$ . Calculated %: C 60.3; H 5.9; N 7.4. The acetate of this product had mp 282-283° (from alcohol) [2].

<u>4-Methyl-5,6-dihydroxy-8-morpholino-2-quinolone (IVa).</u> Morpholine [0.5 ml (6.3 mmole)] was added with stirring under nitrogen to a suspension of 1.0 g (5.7 mmole) of IIIa in 20 ml of methanol at 20-22°. The quinone dissolved and a precipitate immediately began to form. After 1.5 h the precipitate was filtered, washed with methanol and ether, and dried to give 1.3 g (93%) of a product which decomposed at 238-239° (from alcohol). The substance was stable under nitrogen in the dark. Found %: C 60.8; H 6.2; N 9.7.  $C_{14}H_{16}N_2O_4$ . Calculated %: C 60.9; H 5.8; N 10.1. The acetate had mp 186-187° (from alcohol). Found %: C 60.4; H 5.5; N 7.9.  $C_{18}H_{20}N_2O_6$ . Calculated %: C 60.4; H 5.1; N 7.8.

 $\frac{3-n-Butyl-4-chloro-5,6-dihydroxy-8-morpholino-2-quinolone (IVb).}{IIIb in a manner similar to that used to obtain IVa and had mp 243-244° (decomp., from alcohol).} Found %: C 57.7; H 6.1; Cl 10.0; N 8.0. C<sub>16</sub>H<sub>22</sub>ClN<sub>2</sub>O<sub>4</sub>. Calculated %: C 57.9; H 6.0; Cl 10.1; N 7.9.$ 

<u>General Method for the Oxidation of I-IV</u>. The compound to be oxidized (10 mmole) was introduced into a solution of cupric acetate in a mixture of 15 ml of methanol and the amine (Table 1), and the mixture was stirred under oxygen until gas absorption ceased. The reaction mass was treated according to one of the following methods. A. (for Va-e). Water (100 ml) was added, the unchanged starting substance was removed by filtration, and the filtrate was cooled to 5° and neutralized with 10% acetic acid. The precipitate was filtered, washed with water, and transferred into 11 mmole of the appropriate amine in 60 ml of water. The mixture was then treated with charcoal and precipitated with 10% acetic acid.

B. (for Vf-h). The mixture was acidified at 5° with 4 N HCl and extracted with chloroform (three 30ml portions). The extract was washed with water until a neutral reaction was obtained, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized from an appropriate solvent.

Quinones V are red or dark-red, crystalline substances that are soluble in alcohol and acetic acid and also in aqueous solutions of secondary amines and bicarbonate, moderately soluble in acetone, chloroform, and ethyl acetate, slightly soluble in water and benzene, and insoluble in ether and petroleum ether. They gradually decompose in solution and on standing in light (Table 1).

<u>Morpholine Salt of 4-Methyl-8-morpholino-2-quinolone-5,6-quinone.</u> Compound Vb [0.54 g (2 mmole)] was suspended in 7 ml of methanol containing 0.45 g (6 mmole) of morpholine at 20-22°. Compound Vb dissolved at first, and then a precipitate formed while the solution was stirred; this was filtered, washed with

alcohol and ether, and dried to give 0.28 g of red crystals. An additional 0.26 g of product was obtained by evaporation of the filtrate in vacuo to half its original volume and precipitation with ether. The total yield of product was 0.54 g (80%). It had mp 143-144° (from alcohol) and was obtained in the form of red crystals that were quite soluble in water and alcohol, moderately soluble in methanol, slightly soluble in benzene, and insoluble in ether. Found %: C 59.9; H 6.0; N 12.0.  $C_{14}H_{14}N_2O_4 \cdot C_4H_9NO$ . Calculated %: C 59.8; H 6.4; N 11.6. IR spectrum, cm<sup>-1</sup>: 1605 (s), 1625 (s).

 $\frac{4-\text{Methyl-6-hydroxy-2-quinolone-5,8-quinone (VIa).}{A \text{ solution of } 0.88 \text{ g} (22 \text{ mmole}) \text{ of sodium}}$ hydroxide in 10 ml of water was added to 2.7 g (10 mmole) of Va (or an equivalent amount of Vb or Vc) and the mixture was boiled for 5 min. The reaction mass was then cooled and acidified to pH 4 with 4 N HCl. The precipitate was filtered, washed with water, and dried to give 1.6 g (68%) of product. To purify it, the substance was dissolved in excess aqueous sodium bicarbonate, treated with charcoal, and precipitated with 4 N HCl to give a yellow substance with mp > 350° (from water) that was soluble in dimethylformamide, slightly soluble in water, alcohol, acetic acid, and dioxane, and insoluble in chloroform. Found %: C 58.8; H 3.8; N 6.8. C<sub>10</sub>H<sub>7</sub>NO<sub>4</sub>. Calculated %: C 58.5; H 3.5; N 6.8. IR spectrum, cm<sup>-1</sup>: 1540 (s), 1600 (shoulder), 1625 (s), 1680 (shoulder), 3270 (s). UV spectrum (in alcohol):  $\lambda_{max} 228$ , 320 nm (log  $\varepsilon$  4.06, 4.12).

<u>3-n-Butyl-4-chloro-6-hydroxy-2-quinolone-5,8-quinone (VIb)</u>. This was obtained in 85% yield from Ve or Vf in a manner similar to that used to obtain VIa. It was anorange, crystalline substance with mp 242-243° (from acetic acid) that was moderately soluble in alcohol and acetic acid, and insoluble in chloroform, benzene, and ether. Found %: N 5.0; Cl 12.3.  $C_{13}H_{12}ClNO_4$ . Calculated %: N 5.0; Cl 12.5. IR spectrum, cm<sup>-1</sup>: 1530 (m), 1584 (s), 1631 (s), 1675 (shoulder), 3250 (s). UV spectrum:  $\lambda_{max} 255$ , 325 nm (log  $\epsilon$  4.10, 4.24).

<u>General Method for Obtaining Phenazines (VII)</u>. o-Phenylenediamine (3 mmole) was added to a hot solution of 2 mmole of the quinone (V or VIb) in 10-15 ml of alcohol (or acetic acid), the solution was refluxed for 5-10 min, cooled, and the precipitate was filtered after 2 h. If a precipitate did not form, the solution was evaporated in vacuo and the residue was recrystallized. The yields were 60-90%. All of the phenazines were yellow, crystalline substances.

To obtain phenazine VIIi, 0.2 g (1 mmole) of VIa was dissolved by heating in 3 ml of 5% sodium bicarbonate, and 10 ml of acetic acid and 0.12 g (1.1 mmole) of o-phenylenediamine were added rapidly to the hot solution. The precipitate resulting on cooling was filtered, washed with water, a loohol and ether, and dried to give a reddish-orange substance that was insoluble in water and slightly soluble in most organic solvents. The results are presented in Table 2. The structures of compounds VII were confirmed by the results of elementary analysis.

All of the compounds were dried over  $P_2O_5$  and paraffin in vacuo at 50°. The course of the reactions and the purity of the compounds were monitored by means of TLC on silica gel in a chloroform-methanol system (20:1). The IR spectra were obtained in mineral oil mulls with a UR-20 spectrophotometer. The UV spectra in alcohol were obtained with an SF-4 spectrophotometer.

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